rather specific interactions rather than a nonspecific interaction at hydrophobic regions. This is consistent with the inability of the 1,9-dideoxy derivative to antagonize forskolin's activation of adenylate cyclase.

One of the aims of this study was to determine if the potency of forskolin in activating adenylate cyclase could be increased by appropriate derivatization. Although a number of derivatives of forskolin were active, there were none with greater potency than the native molecule. The results of this study do, however, allow characterization of the binding site in terms of the rank order of potency of the partially active species. This could be used to establish a correlation between the initiation of a physiological process induced by forskolin and its derivatives with the activation of adenylate cyclase. Furthermore, a number of inactive derivatives of forskolin are identified that are not grossly different in structure from forskolin, and these can be used as controls in assessing nonspecific effects due to the diterpenoid structure. The similarity of the data on the activity of forskolin derivatives with brain and heart adenylate cyclase, while limited, suggests that the forskolin site may be relatively invariant in different tissues and species (rat, rabbit and guinea pig).

Experimental Section

Biological Test Procedures. Rat cerebral cortex membranes were prepared as described previously.[7] Briefly, rat cerebral cortex was removed from male Sprague–Dawley rats (150–175 g) and chilled briefly in ice-cold Krebs–Ringer bicarbonate glucose buffer (KRB). The tissue was homogenized in ice-cold (50 mM) Tris-HCl buffer, pH 7.5, 0.1 mM $CaCl_2$, in a Dounce homogenizer. The homogenate was centrifuged at 10000*g* for 10 min, and the pellet was washed once in ice-cold buffer, centrifuged, and resuspended in ice-cold 50 mM Tris-HCl, pH 7.5, 0.1 mM $CaCl_2$. Fresh membranes were used in all experiments. Adenylate cyclase experiments were carried out as described previously.[10] Incubations were in a total volume of 250 μL containing 50 mM Tris-HCl buffer, pH 7.5, 1.0 mM 3-isobutyl-1-methylxanthine, 5 mM $MgCl_2$, 0.1 mM ATP, and 0.2 mM EGTA. Each assay contained 2 μCi of [α^{32}-P]ATP and a nucleotide-regenerating system of 5 units creatine phosphokinase and 2 mM creatine phosphate. Assays were initiated by the addition of 25 μL of membranes (~100 μg of membrane protein), were carried out at 30 °C for 10 min, and were terminated by the addition of 0.5 mL of 10% trichloroacetic acid. Carrier cyclic AMP, 0.25 mL of 1 mM cyclic AMP, was added, and radioactive cyclic AMP was isolated and analyzed as described by Salomon et al.[15] Assays were carried out in triplicate. The EC_{50}'s for activation were taken from at least two determinations over a concentration range from 0.01 to 200 μM of the derivative. The EC_{50}'s for the determinations did not vary more than 20%. Adenylate cyclase activity in rabbit cardiac membranes was assayed as described.[4]

A brain vesicular preparation was obtained from male NIH strain guinea pigs (300 g) as described by McNeal et al.[13] Briefly, the method was as follows. Immediately upon removal, the brain was placed on an ice-cooled petri dish and slices of gray matter were cut by hand from the cerebral cortex. The slices weighing about 1.0 g were homogenized by hand in an all-glass homogenizer containing 10 volumes (10 mL/1 g wet weight) of Krebs–Ringer–bicarbonate–glucose buffer (KRB), pH 7.4, preequilibrated with a mixture of 95% O_2–5% CO_2. This homogenate was then centrifuged at 1000*g* for 15 min at 4 °C, and the supernatant was discarded. An aliquot of the vesicular preparation (5 mL) was incubated with 125 μCi of [^{3}H]adenine (specific activity 16.6 Ci/mmol) for 30 min at 37 °C in KRB. The preparation was centrifuged for 5 min at 1000*g*, washed once with cold buffer, and resuspended in 5 mL of cold buffer. This preparation was postincubated for 15 min at 37 °C, washed once, and resuspended in 5 mL of cold KRB. Aliquots (0.2 mL) of the preparation were placed in test tubes and allowed to equilibrate at 37 °C for 10 min. Agents were added in 50-μL aliquots, and the tubes were incubated an additional 10 min at 30 °C. The incubation was stopped with 0.5 mL of 10% trichloroacetic acid, and 0.25 mL of 2 mM cyclic AMP was added as carrier. After centrifugation, 50 μL of the supernatant was removed to determine the amount of total radioactive adenine nucleotides. Radioactive cyclic AMP was determined in the remaining 0.95 mL of supernatant by the method of Salomon et al.[15] Activity is expressed as the percent conversion of total radioactive adenine nucleotide to radioactive cyclic AMP and is the average plus or minus SEM of duplicate determinations.

Registry No. 1, 66575-29-9; 2, 81873-09-8; 3, 84048-20-4; 4, 84048-19-1; 5, 84010-23-1; 6, 84010-21-9; 7, 84010-20-8; 8, 64657-20-1; 9, 64657-21-2; 10, 81873-07-6; 11, 64657-18-7; 12, 84048-28-2; 13, 64657-23-4; 14, 81826-83-7; 15, 84011-60-9; 16, 81873-10-1; 17, 84011-61-0; 18, 84048-29-3; 19, 81873-15-6; 20, 64657-24-5; 21, 81826-89-3; adenylate cyclase, 9012-42-4; cyclic AMP, 60-92-4.

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Ferric Ion Sequestering Agents. 11. Synthesis and Kinetics of Iron Removal from Transferrin of Catechoyl Derivatives of Desferrioxamine B[1]

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Two catechoyl derivatives of desferrioxamine B have been synthesized. The more soluble *N*-(2,3-dihydroxy-4-carboxybenzoyl)desferrioxamine B derivative was found to remove iron from the human iron transport protein transferrin with a pseudo-first-order rate constant of 8.2×10^{-4} min^{-1} (0.2 mM ligand concentration). These results indicate that, unlike desferrioxamine B (Desferal) itself, the synthetic monocatechoyl derivative *is* kinetically able to remove transferrin-bound iron. The possible use of these derivatives in the treatment of transfusion-induced iron overload is discussed.

In previous papers in this series we have described the synthesis and characterization of catechol-based iron chelating agents.[2,3] The purpose of this research has been the formulation of drugs capable of removing excess iron from the bodies of iron-overloaded patients and which (ideally) are orally effective. There is an acute need for such agents in the treatment of the iron overload that

(1) Previous paper in this series: Kappel, M. J.; Raymond, K. N. *Inorg. Chem.* **1982**, *21*, 3437–3442.
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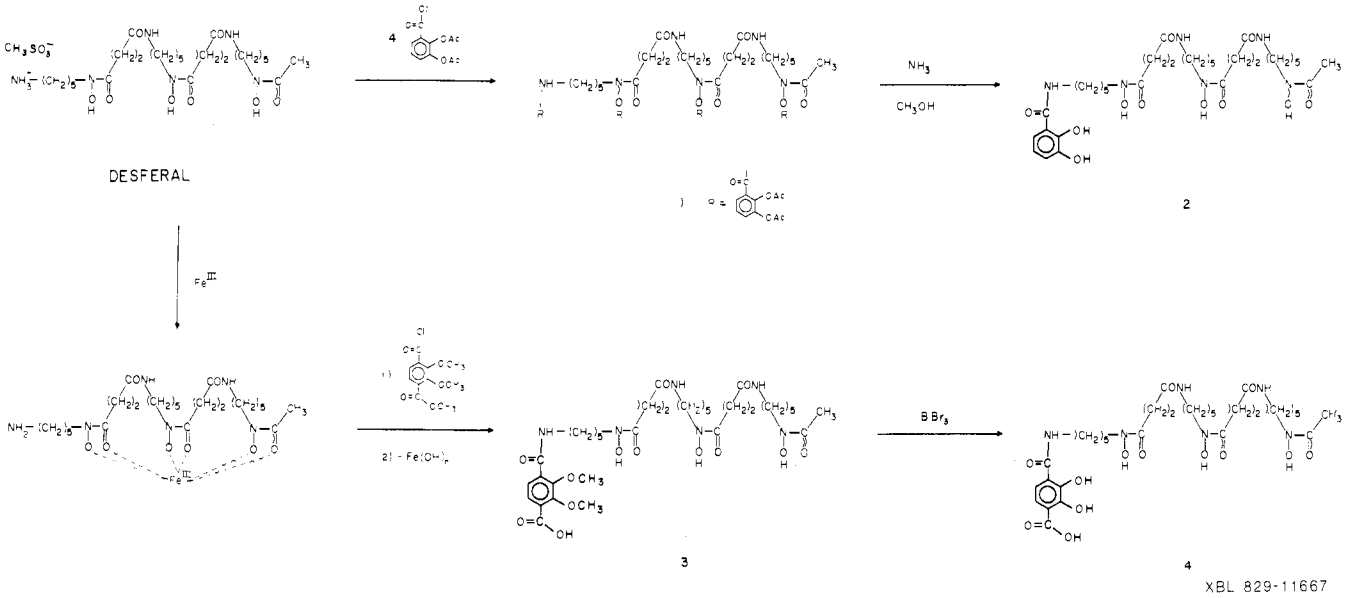
Scheme I. Synthesis of Catechoyl Derivatives of Desferrioxamine B



results from the transfusion therapy required by individuals suffering from the genetic disease β-thalassemia major.[4]

The current drug of choice for the treatment of transfusional iron overload is Desferal, the mesylate salt of the trihydroxamate siderophore desferrioxamine B. While Desferal has been shown to induce increased iron excretion and reduce liver iron in β-thalassemic patients when administered over a period of years,[5] its drawbacks include a lack of oral activity and a short body retention time, which necessitates its administration by the cumbersome and expensive methods of slow subcutaneous or intraveneous infusion. In an attempt to improve the clinical properties of desferrioxamine B, Bickel et al. prepared a number of derivatives in which acyl groups were attached to the terminal amino group of desferrioxamine B.[6] None of these derivatives had any extra chelating abilities and apparently did not increase the drug's iron-removing properties in vivo.

A frequently used criterion for evaluating the possible medical efficacy of an iron-chelating agent is its ability to remove iron from transferrin, the mammalian iron transport protein. Catechol-based siderophores and synthetic analogues are both thermodynamically and kinetically capable of removing transferrin bound iron.[7,8] In contrast, Desferal, although thermodynamically capable, is kinetically slow in removing transferrin iron both in vivo and in vitro,[9,10] a property that may be common to all hydroxamate siderophores. In an attempt to make transferrin-bound iron kinetically available for chelation, we have attached single catechol groups to the terminal amino group of desferrioxamine B. The synthesis and kinetics of iron removal from transferrin of two such derivatives is reported here.

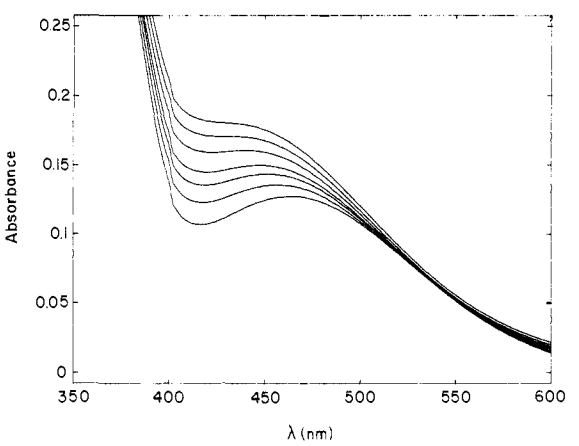


Figure 1. Spectral changes associated with exchange of transferrin-bound iron with compound 4 ([lig] = 2.0×10^{-4} M; [Fe_2Tf] = 2.9×10^{-5} M; pH 7.4; T = 25 °C. The lowest curve is the initial (differic transferrin) spectrum; the upper curve is the spectrum of the fully formed ferric complex of 4.

General Procedure. The 2,3-dihydroxybenzoyl derivative of desferrioxamine B was synthesized by a number of routes differing in either the choice of the catechol protecting groups (methyl, benzyl, acetyl) or the extent of acylation [tetraacylation followed by aminolysis or monoacylation with transient Fe(III) protection of the hydroxamate oxygens]. The method of choice (Scheme I) employed acetyl protection of the catechol and tetraacylation, since the acetyl groups are removed during the aminolysis reaction. Acylation of Desferal with 4 equiv of 2,3-diacetoxybenzoyl chloride under Schotten–Baumann conditions yielded the *N,O,O',O''*-tetrakis(2,3-diacetoxybenzoyl)desferrioxamine B derivative, 1. Saturation of a methanol solution of 1 with ammonia simultaneously cleaved the *O,O',O''*-2,3-diacetoxybenzoyl linkages and removed the acetyl protecting groups to yield the desired product *N*-(2,3-dihydroxybenzoyl)desferrioxamine B (2).

Due to the scarcity of the methyl 2,3-dimethoxy-4-(chloroformyl)benzoate, the synthesis of *N*-(2,3-dihydroxy-4-carboxybenzoyl)deferrioxamine B utilized the transient protection of the hydroxamate oxygens by Fe(III) complexation. The Fe(III) complex of Desferal was acy-

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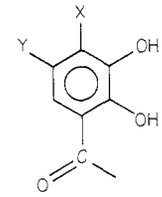
Table I. Relative Kinetic Ability of Fe Removal from Ferric Transferrin



R_1 X = Y = H
R_2 X = H; Y = SO_3^-
R_3 Y = H; X = CO_2^-

ligand	formula[a]	ligand concn, mM	% Fe removed (30 min)	k_2(ligand)/ k_2(Desferal)
enterobactin	$[-CH_2OC(O)CH(NHR_1)-]_3$	0.2[b]	6	120
MECAM	(1,3,5-trisubstituted)$C_6H_3(CH_2NHR_1)_3$	0.2[b]	13	260
3,4-LICAMS	$R_2NH(CH_2)_3NR_2(CH_2)_4NHR_2$	8.0[b]	50	
		0.2[b]	6	120
3,4-LICAMC	$R_3NH(CH_2)_3NR_3(CH_2)_4NHR_3$	0.2[c]	6	260
2	see Figure 1	0.1[c]	2	180
4	see Figure 1	1.2[c]	18	
		0.2[c]	3	130
Desferal	see Figure 1	20.0[b]	5	1
EDTA	$(O_2^-CCH_2)_2N(CH_2)_2N(CH_2CO_2^-)_2$	500.0[b]	37	
		0.2[b]	0	
DMBS	$(CH_3)_2NR_2$	8.0[b]	36	

[a] See structure over column heads. [b] [Fe(Tf)] ≈ 0.16 mM. [c] [Fe(Tf)] ≈ 0.058 mM.

lated with 1 equiv of methyl 2,3-dimethoxy-4-(chloroformyl)benzoate. The Fe(III) was removed by precipitation at high pH (with concomitant hydrolysis of the methyl ester) and the product *N*-(2,3-dimethoxy-4-carboxybenzoyl)desferrioxamine B (**3**) was precipitated at low pH. The methyl protecting groups were removed with BBr_3, yielding the desired product *N*-(2,3-dihydroxy-4-carboxybenzoyl)desferrioxamine B (**4**).

Results and Discussion

Kinetics. The spectral changes associated with the addition of a solution of *N*-(2,3-dihydroxy-4-carboxybenzoyl)desferrioxamine B (**4**) to a solution of diferric transferrin are shown in Figure 1. The 466-nm absorption maximum of diferric transferrin shifts smoothly to a spectrum identical with one of the 1:1 Fe(III) complex of **4** at pH 7.4.[11] This indicates iron was removed from transferrin by the ligand. A plot of $-\ln (A_t - A_\infty)/(A_0 - A_\infty)$ vs. time (Figure 2) gives a pseudo-first-order rate constant, k_{obsd}, equal to 8.2×10^{-4} min^{-1} at a ligand concentration of 0.2 mM. After 30 min, 3% of the transferrin iron had been removed at a ligand to transferrin ratio of 7:1 (Table I). At the limit of its solubility (≤0.1 mM, lig/Tf = 3.5:1), *N*-(2,3-dihydroxybenzoyl)desferrioxamine B (**2**) was able to remove approximately 2% of the transferrin iron after 30 min. These results can be more easily compared to Desferal in terms of a second-order rate constant, k_2. At low ligand concentrations, the rate expression for iron removal from transferrin reduces to $R = k_2$[FeTf][lig]. By dividing the "initial rate" (i.e., the percentage of iron removed after 30 min) by the initial ferric transferrin and ligand concentrations, a rough estimate of k_2 for each ligand can be obtained. The ratio of k_2 (lig)/k_2 (Desferal) is then a measure of the "relative effectiveness" of iron removal from transferrin as compared to Desferal.

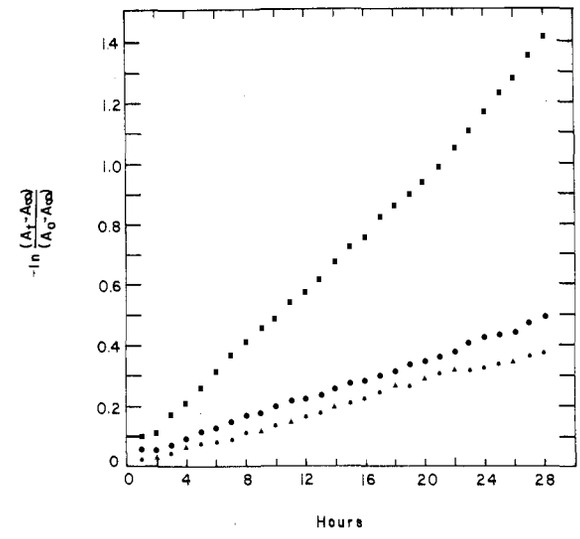


Figure 2. Plot of $-\ln (A_t - A_\infty)/(A_0 - A_\infty)$ vs. time for the removal of iron from transferrin by Desferal and the synthetic catechoyl derivatives: (■) **4** (0.2 mM), (●) **3** (1.2 mM), (▲) Desferal (1.2 mM).

As seen in Table I, the two catechoyl derivatives of desferrioxamine B are greater than 100 times more effective at iron removal than Desferal. This is roughly the same order of magnitude as that of the tricatechol ligands. It is interesting to note that the methyl-protected derivative **3**, which is unable to bind Fe(III) via the catechol oxygens, removed iron from transferrin at the same low rate as Desferal (Figure 2).

The addition of a single catechol moiety to desferrioxamine B removes the kinetic barrier of this hydroxamate siderophore to iron removal from transferrin. By making transferrin-bound iron kinetically available for chelation, these monocatechoyl derivatives of desferrioxamine B may prove to be more effective than Desferal at inducing iron excretion in man. Compounds **2** and **4** are currently being investigated for their pH-dependent modes of Fe(III) coordination and their effectiveness at iron removal in vivo.

(11) This spectrum is different from a tris(hydroxamate)–ferric complex and, thus, indicates that the catechol group is coordinated in at least a significant fraction of the Fe(III) complexes. The pH-dependent equilibria between the various forms of the Fe(III)–**4** complex are under study.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM390 spectrometer with Me_4Si as internal reference. Solvent was removed under vacuum (rotovap). Thin-layer chromatography was performed on precoated Analtech silica gel sheets GHLF which were developed with 15% MeOH in CH_2Cl_2 and visualized by UV, I_2, or Fe(III)/MeOH spray. Microanalyses were performed by the Analytical Services, Chemistry Department, University of California, Berkeley. Diacetoxybenzoyl chloride was prepared by the method of Bergeron.[12] Methyl 2,3-Dimethoxy-4-(chloroformyl)benzoate was prepared by the method of Weitl.[3]

Kinetics. Apotransferrin (Sigma Chemical Co.) was saturated by the procedure of Bates et al. with a fresh $Fe(NTA)_2^{3-}$ solution followed by gel filtration on two preequilibrated Sephadex G-25 resins eluted with 0.1 M $NaClO_4$ and 0.1 M Tris-HCl (pH 7.4).[13] The ratios $A_{280}/A_{466} \leq 24$ and $A_{428}/A_{466} = 0.85$ indicate ≥95% saturation. Ligand solutions in 0.1 M Tris-HCl (pH 7.4) were freshly prepared by heating slightly until the ligand dissolved and then cooled to 25.0 °C. Half-milliliter aliquotes each of ligand and diferric transferrin solutions were mixed in a thermostated quartz cell maintained at 25.0 °C. Visible spectra were taken on a Hewlett Packard 8450A UV/Vis spectrophotometer. Linear plots of $-\ln(A_t - A_\infty)/(A_0 - A_\infty)$ vs. time at 426 nm were obtained over 2 half lives. The value of k_{obsd} was obtained by linear least-squares analysis.

***N*-(2,3-Dihydroxybenzoyl)desferrioxamine B (2).** Solutions of 2,3-diacetoxybenzoyl chloride (8.784 g, 34 mmol) in 400 mL of CH_2Cl_2 and 500 mL of saturated $NaHCO_3$ were added simultaneously over 0.5 h to a vigorously stirred solution of Desferal (5.00 g, 8 mmol) in 75 mL of water on an ice bath. After 1.5 h an additional 100 mL of saturated $NaHCO_3$ was added. Upon completion of the reaction after 2.5 h, 800 mL of CH_2Cl_2 was added, and the layers were separated. The aqueous layer was extracted with two 100-mL portions of CH_2Cl_2, and then the combined organic layers were washed with two portions of 0.5 M HCl (250 mL) and dried (Na_2SO_4). Evaporation of the solvent yielded a foam, which was then dissolved in 250 mL of MeOH, degassed in vacuo, and put under N_2. The solution was saturated with NH_3 gas for 10 min and then evaporated. To remove NH_3, methanol was added to the residue and then removed under vacuum (several times). Recrystallization from MeOH afforded 4.389 g (85%) of off-white powder: mp 178–178.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.0–1.8 (br m, 18 H), 1.9 (s, 3 H), 2.3 (br t, 4 H), 2.6 (br t, 4 H), 2.9–3.2 (br m, 4 H), 3.2–3.7 (br m, 8 H), 6.7 (t, 1 H), 6.95 (d, 1 H), 7.3 (d, 1 H), 7.8 (br t, 2 H), 8.8 (br t, 1 H), 9.1 (br s, 1 H), 9.6 (br s, 3 H). Anal. Calcd for $C_{32}H_{52}N_6O_{11}\cdot H_2O$: C, 53.74; H, 7.63; N, 11.76. Found: C, 53.65; H, 7.23; N, 11.64.

***N*-(2,3-Dimethoxy-4-carboxybenzoyl)desferrioxamine B (3).** Solutions of methyl 2,3-dimethoxy-4-(chloroformyl)benzoate (2.189 g, 8 mmol) in 150 mL of ether and 20 mL of 0.5 M NaOH were added simultaneously over 0.5 h to a vigorously stirred solution of Desferal (5.00 g, 8 mmol) and $FeCl_3$ (1.297 g, 8 mmol) in 100 mL of H_2O and 60 mL of 0.5 M NaOH on an ice bath. Over the next 1.5 h, 10 mL of 0.5 M NaOH were added to keep the pH above 9. The layers were separated, and the ether layer was washed with 50 mL of H_2O twice. The combined aqueous layers were reduced in volume by about one-half and then basified with 4 M NaOH to pH 12. The resulting ferric hydroxide was removed by filtration through a Metricel 0.45-μm filter. Acidification was 6 M HCl to pH 2 yielded a white precipitate, which was recrystallized from MeOH to give 5.297 g (94%) of white powder: mp 146.5–148.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.0–1.7 (br m, 18 H), 1.9 (s, 3 H), 2.2 (br t, 4 H), 2.45 (br t, 4 H), 2.7–3.1 (br m, 4 H), 3.1–3.5 (br m, 8 H), 3.75 (s, 6 H), 7.23 (d, 1 H), 7.40 (d, 1 H), 7.7 (br t, 2 H), 8.2 (br t, 1 H). Anal. Calcd for $C_{35}H_{56}N_6O_{13}$: C, 54.64; H, 7.36; N, 10.97. Found: C, 54.82; H, 7.41; N, 10.80.

***N*-(2,3-Dihydroxy-4-carboxybenzoyl)desferrioxamine B (4).** A solution of BBr_3 (0.50 mL, 5.3 mmol) in 20 mL of CH_2Cl_2 was added to **3** (0.9212 g, 1.2 mmol) suspended in 10 mL of CH_2Cl_2 over 5 min while on an ice bath under N_2. After 6 h, 50 mL of H_2O was added, and the reaction mixture was stirred for 2 h. The liquids were decanted. To remove the volatile borates, methanol was added to the gum adhering to the walls of the reaction flask and then removed under vacuum (three times). Recrystallization from MeOH afforded 0.5031 g (57%) of white solid: mp 169–171 °C; ^1H NMR (Me_2SO-d_6) δ 1.0–1.7 (br m, 18 H), 1.9 (s, 3 H), 2.2 (br t, 4 H), 2.5 (br t, 4 H), 2.7–3.1 (br m, 4 H), 3.1–3.5 (br m, 8 H), 7.2 (d, 1 H), 7.36 (d, 1 H), 7.7 (br m, 2 H), 8.8 (br m, 1 H), 9.5 (br m, 2 H). Anal. Calcd for $C_{33}H_{52}N_6O_{13}\cdot H_2O$: C, 52.21; H, 7.19; N, 11.07. Found: C, 51.99; H, 6.88; N, 10.95.

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Registry No. 1, 84010-58-2; 2, 84010-59-3; 3, 84010-60-6; 4, 84010-61-7; Desferal, 70-51-9; 2,3-diacetoxybenzoyl chloride, 65055-19-8; methyl 2,3-dimethoxy-4-(chloroformyl)benzoate, 75956-64-8; ferrioxamine B, 14836-73-8; Fe, 7439-89-6.

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Synthesis of (*E*)-1-(5-Chlorothien-2-yl)-2-(1*H*-imidazol-1-yl)ethanone 2,6-Dichlorophenylhydrazone Hydrochloride, a Novel, Orally Active Antifungal Agent

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The preparation, determination of isomeric configuration, and antifungal properties of (*E*)-1-(5-chlorothien-2-yl)-2-(1*H*-imidazol-1-yl)ethanone 2,6-dichlorophenylhydrazone hydrochloride (1) are described. In vitro, compound 1 has been shown to have activity against *Candida albicans* comparable with miconazole. When administered orally to animals with experimentally induced vaginal candidiasis or systemic candidiasis, compound 1 produced results approaching those produced by ketoconazole. In addition, topical administration of compound 1 to rats with vaginal candidiasis produced results comparable with those produced by similar administration of clotrimazole. Unlike ketoconazole, which is active by a mechanism that is essentially fungistatic, compound 1 shares with miconazole a mode of action that is fungicidal. However, unlike miconazole, compound 1 exhibits activity following oral administration. Compound 1 has been found to be negative in the Ames test.

Ketoconazole[1] is at present the only imidazole-based antifungal agent that can be used orally in the treatment of systemic fungal infections in man. Other imidazole-based antifungal agents, such as miconazole, econazole,[2]

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