82–84 °C (0.5 mm)], 4-OCH_3 [mp 47–48 °C (pentane)], and 3,4-OCH_2O [mp 49–50 °C (pentane)] methyl benzoate derivatives and the 2,4-Cl_2 [bp 83–85 °C (0.2 mm)] and 3,4-Cl_2 [bp 137–139 °C (10 mm)] ethyl benzoate derivatives.

The purity of these esters was confirmed by GLC and ^1H NMR. The esters used to prepare compounds **4a,d,j,n–q** were obtained from Aldrich Chemical Co.

5-Aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols (4). General Procedure. A stirred solution of 8.0 g (0.05 mol) of 2-(*o*-methylphenyl)imidazoline in 200 mL of dry THF maintained under a N_2 atmosphere was treated dropwise with 105 mL (0.15 mol *n*-BuLi) of 1.6 M *n*-BuLi in hexane and then heated to 35 °C for ca. 4 h. The mixture was then immersed in a dry ice–acetone bath, cooled to an internal temperature of −25 °C, and treated dropwise with 0.10 mol of methyl or ethyl aryl ester **6** at such a rate that the temperature did not exceed −20 °C. After an additional 3 h at −20 °C, the reaction mixture was allowed to warm to 0 °C and then treated with 30 mL of saturated NH_4Cl solution. After standing overnight at room temperature, the mixture was concentrated in vacuo and then treated with 200 mL of CH_2Cl_2 and 100 mL of H_2O. The CH_2Cl_2 layer was separated, washed with H_2O, dried with anhydrous $MgSO_4$, and filtered, and the filtrate was then concentrated to give a solid that was crystallized from the appropriate solvent given in Table II.

Acknowledgment. The authors are grateful to Nancy Engstrom and Urs Stoeckli for instrumental determinations and to William Bonkoski for the microanalyses.

Registry No. **4a**, 56882-45-2; **4b**, 84774-99-2; **4c**, 56882-43-0; **4d**, 56882-41-8; **4e**, 56882-50-9; **4f**, 84775-00-8; **4g**, 56882-42-9; **4h**, 56882-51-0; **4i**, 56882-49-6; **4j**, 56882-46-3; **4k**, 56882-44-1; **4l**, 56882-47-4; **4m**, 56882-48-5; **4n**, 83634-04-2; **4o**, 60151-19-1; **4p**, 60099-37-8; **4q**, 60099-38-9; **5**, 8363-39-9; **6** (Ar = 2-FC_6H_4; R = CH_3), 394-35-4; **6** (Ar = 3-FC_6H_4; R = CH_3), 455-68-5; **6** (Ar = 2-ClC_6H_4; R = CH_3), 610-96-8; **6** (Ar = 3-ClC_6H_4; R = CH_3), 2905-65-9; **6** (Ar = 4-ClC_6H_4; R = CH_3), 1126-46-1; **6** (Ar = 3-$CF_3C_6H_4$; R = CH_3), 2557-13-3; **6** (Ar = 4-$CH_3OC_6H_4$; R = CH_3), 121-98-2; **6** (Ar = 3,4-$OCH_2OC_6H_4$; R = CH_3), 326-56-7; **6** (Ar = 2,4-$Cl_2C_6H_3$; R = CH_2CH_3), 56882-52-1; **6** (Ar = 3,4-$Cl_2C_6H_3$; R = CH_2CH_3), 28394-58-3.

1-[1-[2-[(3-Chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole Hydrochloride, a New Potent Antifungal Agent

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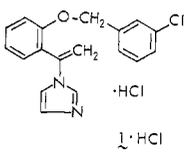
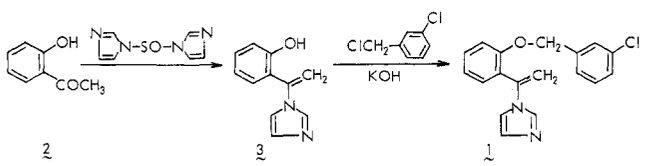
The synthesis and antifungal properties of 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole hydrochloride (1·HCl) are described. Topical application of cream and gel formulation of 1·HCl showed high efficacy against guinea pig dermatophytosis.

Substances[1] containing the imidazole nucleus are known for their antimycotic activity and fall into two general classes: the poly(aryl)methylimidazoles (e.g., clotrimazole[2]) and the arylethylimidazoles (e.g., miconazole[3]). We describe here the preparation and properties of a potent new antifungal agent based on the 1-vinylimidazole skeleton, namely, 1-[1-[2-[(3-chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole hydrochloride (1·HCl), which is at present undergoing clinical investigation.[4]



1·HCl

Chemistry. The 1-vinylimidazole compound **3** was obtained by reaction of *N,N'*-thionyldiimidazole[5] with *o*-hydroxyacetophenone (**2**) in dichloromethane in good yield. Treatment of **3** with *m*-chlorobenzyl chloride in the presence of potassium hydroxide in dimethylformamide afforded **1**. Formation and purification as the hydrochloride salt gave 1·HCl.



2 3 1

Biological Data. In the agar dilution tests on Sabouraud's glucose agar and Bacto-yeast morphology agar, using inocula[6] of 1×10^6 cells per milliliter of yeasts or 1×10^6 conidia per milliliter of moulds and dermatophytes, 1·HCl exhibited a broad spectrum against a wide variety of fungi. 1·HCl inhibited typical dermatophyte species (seven strains of *Trichophyton mentagrophytes*, six of *Trichophyton rubrum*, two of *Microsporum canis*, one of *Microsporum gypseum*, and three of *Epidermophyton floccosum*) at MIC values 0.16–1.25 μg/mL. *Aspergillus spp.* (five strains) and *Penicillium spp.* (two strains) were sensitive at 0.63–5 μg/mL. However, *Candida* yeasts (eight strains of *Candida albicans*, two of *Candida tropicalis*, and one of *Candida guilliermondii*) and other yeasts (two strains

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(5) (a) Ogata, M.; Matsumoto, H.; Kida, S. *Heterocycles* **1979**, *12*, 1285. (b) Ogata, M.; Matsumoto, H., Kida, S.; Shimizu, S. *Tetrahedron* **1979**, *52*, 5011. (c) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S. *Chem. Ind. (London)* **1980**, 85. (d) Ogata, M.; Matsumoto, H.; Shimizu, S. *Heterocycles* **1980**, *14*, 955. (e) Ogata, M.; Matsumoto, H. *Synthetic Commun.* **1980**, *10*, 559. (f) Ogata, M.; Matsumoto, H. *Ibid.* **1980**, *10*, 733. (g) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem. Chim. Ther.* **1981**, *16*, 373. (h) Ogata, M.; Shimizu, S.; Matsumoto, H. *Chem. Ind. (London)* **1982**, 200.
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Table I. In Vitro Activity of 1·HCl and Other Imidazole Antimycotics against Clinically Isolated Strains of Dermatomycosis as Measured on Sabouraud's Glucose Agar[a]

organism[b]	no. of isolates	geometric mean MIC (range), μg/mL clotrimazole	miconazole	econazole	1·HCl
C.a.[c]	44	46.8 (20-80)	28.3 (20-40)	23.0 (20-40)	33.1 (20-80)
T.m.[d]	27	0.75 (0.31-1.25)	4.06 (1.25-10)	0.89 (0.31-2.5)	0.75 (0.31-1.25)
T.r.[d]	102	0.78 (0.16-2.5)	3.31 (0.31-20)	1.09 (0.16-5.0)	0.57 (0.16-2.5)

[a] Inocula of *Candida* strains were adjusted to 1 × 10^6 cells/mL, and inocula of dermatophyte strains were adjusted to 1 × 10^6 conidia/mL as previously described.[6] [b] *C.a.* = *Candida albicans*; *T.m.* = *Trichophyton mentagrophytes*; *T.r.* = *Trichophyton rubrum*. [c] MIC values were read after 2 days of incubation at 37 °C. [d] MIC values were read after 7 days of incubation at 28 °C.

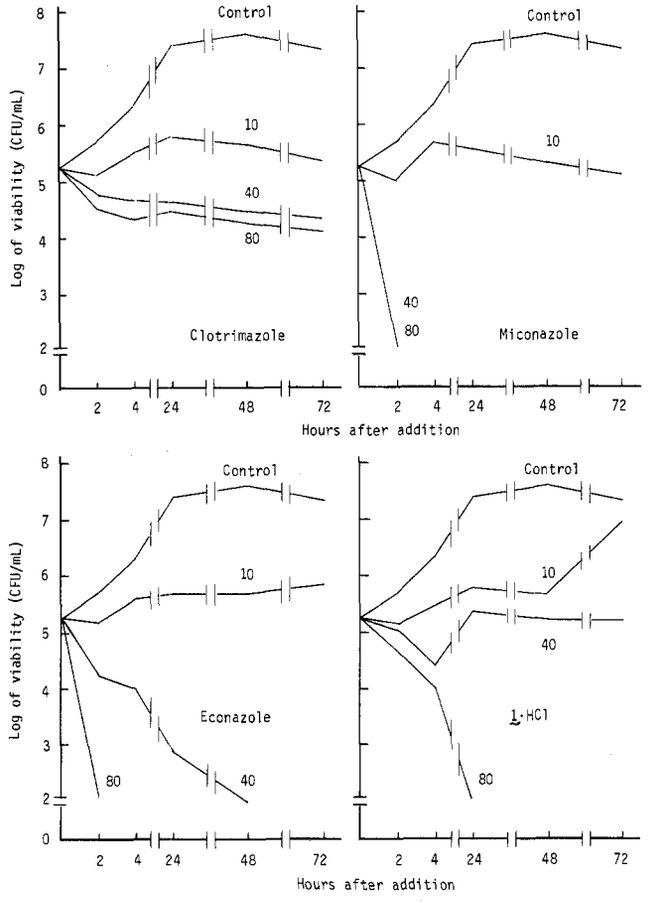

Figure 1. Effect of 1·HCl and other imidazole antimycotics on viability of *C. albicans* IFO 1060 in yeast nitrogen base broth with L-asparagine and glucose. Drugs were added to cultures 3 h after the start of incubation in the indicated concentrations of micrograms per milliliter.

of *Cryptococcus neoformans* and one of *Torulopsis glabrata*) required moderate MIC values of 10 to 80 μg/mL for inhibition.

Susceptibilities to 1·HCl of pathogenic fungal strains freshly isolated from clinical specimens of dermatomycosis were compared with those of other known imidazole antimycotics (Table I). Against 102 isolates of *T. rubrum*, 1·HCl showed a better geometric mean MIC value, 0.57 μg/mL, than other imidazole compounds, which were 0.78–3.31 μg/mL. The mean MIC of 1·HCl against 27 isolates of *T. mentagrophytes* was 0.75 μg/mL, equivalent to that of clotrimazole[2] and almost similar to that of econazole[3a] (0.89 μg/mL). Fourty-four strains of *C. albicans* were more susceptible to econazole and miconazole[3a] than to 1·HCl and clotrimazole. The mean MIC values of econazole (23.0 μg/mL) and miconazole (28.3 μg/mL) were nearly 2-fold lower than that of clotrimazole (46.8 μg/mL). Relative to clotrimazole, 1·HCl (33.1 μg/mL) showed slightly better activity.

Table II. Therapeutic Effect of 1·HCl and Clotrimazole on Experimental Dermatophytosis on Guinea Pigs after Topical Application Once Daily for 9 Consecutive Days, Beginning 5 Days Postinfection

exptl group	no. of sites treated	av of lesion score	skin sections yielding negative culture, no./total (%)
infected control	12	2.75 ± 0.52	0/60[b] (0)
vehicle[a]	12	1.87 ± 0.29	3/60 (5)
1·HCl (1% cream)	12	0.83 ± 0.23	39/60 (65)
clotrimazole (1% cream)	12	0.83 ± 0.23	37/60 (61.7)

[a] Cream vehicle formulated for 1·HCl (1% cream). [b] Five skin sections cut out from each treated site.

Table III. Therapeutic Effect of 1·HCl and Clotrimazole on Experimental Dermatophytosis on Guinea Pigs after Topical Application Once Daily for 11 Consecutive Days, Beginning 4 Days Postinfection

exptl group	no. of sites treated	av of lesion score	skin sections yielding negative culture, no./total (%)
infected control	12	2.91 ± 0.18	0/60[b] (0)
vehicle[a]	12	2.41 ± 0.27	3/60 (5)
1·HCl (1% gel)	12	1.21 ± 0.24	36/60 (60)
clotrimazole (1% tincture)	12	1.33 ± 0.23	12/60 (20)

[a] Gel vehicle formulated for 1·HCl (1% gel). [b] Five skin sections cut out from each treated site.

Fungicidal activity of 1·HCl was compared to those of other imidazole compounds with reference to the killing curves against *C. albicans* with an initial inoculum of 2 × 10^5 cells/mL (Figure 1). 1·HCl was found to be fungicidal at 80 μg/mL. Clotrimazole was not fungicidal at the same concentration. Miconazole showed greater activity relative to econazole, though both compounds were fungicidal at 80 and 40 μg/mL. The killing curves of the four compounds against *T. rubrum* with an inoculum of 5 × 10^5 conidia/mL were also tested (Figure 2). 1·HCl. as well as econazole, was fungicidal at 80 and 40 μg/mL. Clotrimazole and miconazole showed no marked fungicidal activity at the same concentrations.

The topical efficacy of 1% cream and gel forms of 1·HCl was compared with that of 1% clotrimazole cream and tincture, respectively, by application against experimental dermatophytosis on guinea pigs caused by *Trichophyton asteroides*. The cream form of 1·HCl was evaluated to be bioequivalent to clotrimazole cream after 9 consecutive days of treatment initiated 5 days postinfection (Table II). The gel form of 1·HCl was more effective than clotrimazole tincture with respect to the rate of appearance of negative cultures in another curative test where the treatment

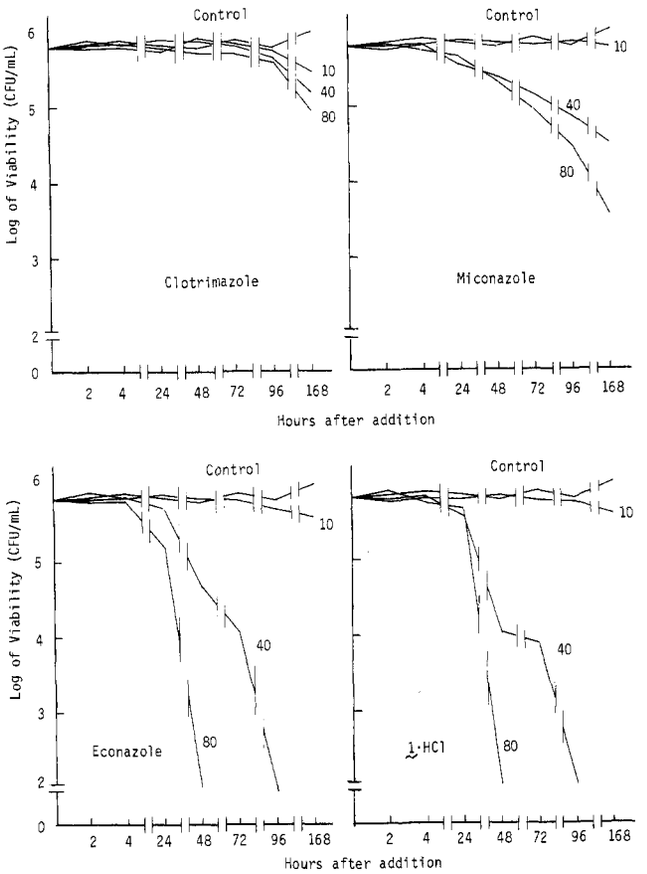

Figure 2. Effect of 1·HCl and other imidazole antimycotics on viability of *T. rubrum* IFO 5808 in yeast nitrogen base broth. Drugs were added to cultures 1 h after the start of incubation in the indicated concentration of micrograms per milliliter.

started 4 days postinfection and continued for 11 days (Table III).

The preliminary acute toxicity study of 1·HCl gave LD_{50} values of 7000 mg/kg sc and 2500 mg/kg po in rats.

The mutagenicity of 1·HCl was assayed in the Ames test against *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-100, and TA-98, as well as *Escherichia coli* strain WP2 HCR(−). No mutagenicity was observed at doses of 5 and 10 μg/plate.

Experimental Section

Melting points were determined in a "Büchi" capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 spectrometer. Elementary analyses were performed by the analytical department of Shionogi Research Laboratories and are within ±0.4% of the calculated values.

1-[1-(2-Hydroxyphenyl)vinyl]-1*H*-imidazole (3). To a solution of imidazole (120 g, 1.763 mol) and dry CH_2Cl_2 (360 mL), was added dropwise, with stirring $SOCl_2$ (52.4 g, 0.440 mol), with the temperature maintained at around 20 °C. After the mixture had been stirred for 10 min, *o*-hydroxyacetophenone (**2**; 50 g, 0.367 mol) was added at 20 °C with stirring. After 30 min at room temperature, the solvent was evaporated at 40 °C and gradually diluted with aqueous K_2CO_3 (K_2CO_3, 73.1 g, 0.529 mol; H_2O, 220 mL), which was gradually added under ice cooling until crystallization of the product was complete. Filtration and washing of the residue with water and acetone gave 51.5 g (75.3%, mp 150–152 °C) of **3**. The analytical sample from isopropyl alcohol had mp 152.5–154 °C; NMR (Me_2SO-d_6) δ 5.08 (1 H, d, J = 1.0 Hz, =CH vinyl), 5.53 (1 H, d, J = 1.0 Hz, =CH vinyl), 6.67–7.55 (7 H, m, aromatics), 9.83 (1 H, br s, OH). Anal. ($C_{11}H_{10}N_2O$) C, H, N.

1-[1-[2-[(3-Chlorobenzyl)oxy]phenyl]vinyl]-1*H*-imidazole Hydrochloride (1·HCl). To a solution of **3** (48.2 g, 0.259 mol) and dry DMF (240 mL) was added, with stirring at room temperature, KOH (20.3 g, 86% purity, 0.362 mol). After the mixture had been stirred for 1 h, *m*-chlorobenzyl chloride (50 g, 0.310 mol) was added with stirring and heated at 50–55 °C for 15 min. The mixture was decomposed with water and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4, and filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel. The fractions eluted with 3% MeOH–CH_2Cl_2 were collected to obtain **1** (mp 72–73 °C, from *n*-hexane). A solution of **1** in AcOEt was treated with dry HCl to give 1·HCl. The precipitate was collected and recrystallized from AcOEt–CH_3CN (1:1) to give 1·HCl (73.7 g, 81.9%): mp 148.5–150 °C; NMR (Me_2SO-d_6) δ 5.13 (2 H, s, CH_2 benzyl), 5.63 (1 H, d, J = 2.0 Hz, =CH vinyl), 6.17 (1 H, d, J = 2.0 Hz, =CH vinyl), 7.07–7.97 (11 H, m, aromatics), 9.50 (1 H, m, ≡NH^+). Anal. ($C_{18}H_{16}Cl_2N_2O$) C, H, Cl, N.

Guinea Pig Dermatophytosis. Male albino guinea pigs, weighing 350 to 400 g, were shorn, and their backs were abraded in areas of about 3 cm^2 in four places. One place was used as the infected control and the other three for separate drug treatments. These four sites were inoculated with a conidia suspension of *Trichophyton asteroides* containing 2.5 × 10^6/0.05 mL. Treatment was given once daily with 0.5 g of commercial clotrimazole 1% cream, formulation of 1·HCl in 1% cream[7] and gel,[8] and 0.4 mL of clotrimazole 1% tincture. Evaluation was made in terms of (a) average lesion score and (b) rate of appearance of negative cultures from infected skin sections. On the 1st day after the last treatment, lesions of the treated sites were graded[9] +1 to +4 according to the intensity of infection. Average lesion scores were calculated on each experimental group. Skin sections were cut out from the treated sites after the animals had been killed by chloroform anesthesia. These sections were cultured on Sabouraud's glucose agar for 7 days at 28 °C.

Acknowledgment. The authors thank Drs. H. Otsuka and T. Komeno (Director of these Laboratories) for their encouragement and permission to publish this work. Thanks are also due to Drs. Y. Harada and Y. Titani of these laboratories for the toxicity and mutagenicity experiments.

Registry No. 1, 77175-51-0; 1·HCl, 77174-66-4; 2, 118-93-4; 3, 74204-47-0; *m*-chlorobenzyl chloride, 620-20-2; *N,N'*-thionyldiimidazole, 3005-50-3.

(7) The cream formulation contained carboxyvinyl polymer, cetanol, 2-octyldodecyl myristate, Span 60, Tween, 60, methyl *p*-hydroxybenzoate, *n*-butyl *p*-hydroxybenzoate, Na_2EDTA, and water.

(8) The gel formulation contained carboxyvinyl polymer, tris(2-hydroxypropyl)amine 2-propanol, propylene glycol, PEG 400, and water.

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