15). **General Method E.** A mixture of the nitrile (**9**, **14a**, or **14c**; 10 mmol), sodium azide (0.85 g, 13 mmol), and ammonium chloride (0.70 g, 13 mmol) in 100 mL of anhydrous DMF was heated at 120–130 °C for either 1 day (for the 2-substituted compounds **9**) or 4 days (for the 3-substituted cases **14a** and **14c**). The reaction mixture was cooled, poured into 500 mL of ice–water, and acidified with concentrated HCl to yield a solid, which was collected by filtration and recrystallized from DMF–water to give the pure tetrazole **10** or **15**.

3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzoxazol-4-one (15b). A mixture of 2-aminobenzoxazole (6.70 g, 50.0 mmol), ethyl 1*H*-tetrazol-5-ylacetate[10] (7.80 g, 50.0 mmol), and triethyl orthoformate (10.0 g, 67.8 mmol) was heated at 120 °C briefly to obtain a stirrable melt. $AlCl_3$ (0.3 g, 2 mmol) was added, and the mixture was heated at 120 °C in an open flask for 40 min. The mixture was cooled and triturated with methanol, and the solid was collected by filtration and washed with methanol to give 10.9 g (73%) of the intermediate ester **17** as a light yellow solid, mp 202–203 °C. This ester (2.00 g, 6.67 mmol) was combined with 8 g of polyphosphoric acid, heated to 140 °C gradually over 1 h, held at 140 °C for 20 min, then cooled somewhat, and treated with 100 mL of water. The resulting solid was collected by filtration, washed thoroughly with water, and dried to give 1.05 g (62%) of yellow solid. Recrystallization from DMF–water gave 0.63 g (37%; 27% overall) of the pure tetrazole **15b**.

Acknowledgment. We thank Prof. R. F. Borch and Dr. J. F. Gerster for helpful discussions and Ms. J. A. Sneitzer for assistance with the manuscript.

Registry No. **4a**, 58099-49-3; **4b**, 69461-78-5; **6a**, 69461-82-1; **6b**, 69461-84-3; **6c**, 69461-85-4; **7a**, 84712-10-7; **7b**, 84712-11-8; **7c**, 84712-12-9; **8a**, 84712-20-9; **8b**, 84712-21-0; **8c**, 84712-22-1; **9a**, 84712-23-2; **9b**, 84712-24-3; **9c**, 84712-25-4; **10a**, 84712-13-0; **10b**, 84712-14-1; **10c**, 84712-15-2; **11a**, 21786-97-0; **11b**, 69461-83-2; **11c**, 50532-94-0; **12a**, 64483-80-3; **12b**, 84712-16-3; **12c**, 84712-17-4; **13a**, 84712-26-5; **13b**, 84712-27-6; **13c**, 84712-28-7; **14a**, 21787-05-3; **14b**, 84712-29-8; **14c**, 84712-30-1; **15a**, 73351-75-4; **15b**, 84712-18-5; **15c**, 84712-19-6; **16**, 13616-37-0; **17**, 84731-12-4; DMAF, 7542-94-1; 2-aminobenzothiazole, 136-95-8; 2-aminobenzoxazole, 4570-41-6; 2-amino-1-methylbenzimidazole, 1622-57-7; diethyl (ethoxymethylene)malonate, 87-13-8; 5-aminotetrazole, 4418-61-5; ammonia, 7664-41-7; triethyl orthoformate, 122-51-0.

Antimycotic Azoles. 6. Synthesis and Antifungal Properties of Terconazole, a Novel Triazole Ketal

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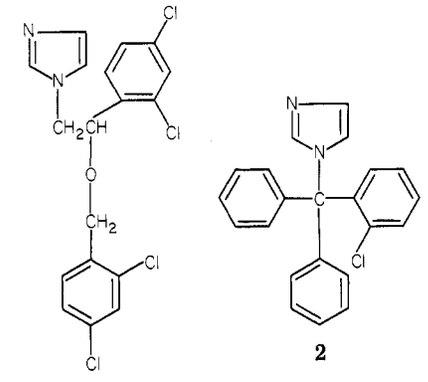
The preparation and antifungal properties of *cis*-1-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine are reported. Terconazole has a high topical in vivo activity against vaginal candidosis in rats and against dermatophytosis in guinea pigs.

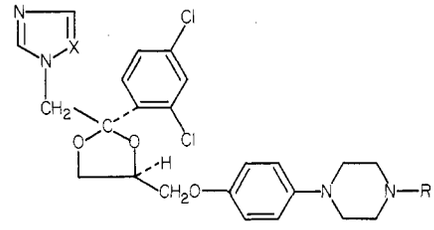
Miconazole (**1**),[1,2] clotrimazole (**2**),[3] and ketoconazole (**3a**)[4,7] are widely used for the treatment of fungal diseases. Unlike miconazole and clotrimazole, ketoconazole is well absorbed in the bloodstream. After oral administration, ketoconazole has been found to be highly effective against crop candidosis in turkeys, vaginal candidosis in rats, systemic candidosis in chickens, systemic and skin candidosis, as well as dermatophytosis, in guinea pigs, and coccidioidomycosis in mice.[6]

As a result of our continuous search for new antifungal agents, in particular azole ketals, having an improved topical activity against superficial fungal infections, we report the synthesis and antifungal properties of terconazole (**3b**), a novel triazole ketal.

Chemistry. The synthesis, starting from *cis*-[2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (**4**),[4] is outlined in Scheme I. The sodium salt of triazole, generated in situ from triazole and NaH dispersion (50%), in mineral oil is coupled with the bromomethyl ketal **4** in Me_2SO at 130 °C to give a mixture of triazole derivatives, which are saponified at reflux temperature with NaOH in dioxane–water to the alcohols **5** and **6**. Pure **5** and **6** are obtained after chromatography



1 **2**



3a, X = CH; R = $COCH_3$
b, X = N; R = $CH(CH_3)_2$

(1) E. F. Godefroi, J. Heeres, J. Van Cutsem, and P. A. J. Janssen *J. Med. Chem.*, **12**, 784 (1969).
(2) J. Van Cutsem and D. Thienpont, *Chemotherapy*, **17**, 392 (1972).
(3) K. H. Büchel, W. Draber, E. Regel, and M. Plempel, *Arzneim.-Forsch.*, **22**, 1260 (1972).
(4) J. Heeres, L. J. J. Backx, J. H. Mostmans, and J. Van Cutsem, *J. Med. Chem.*, **22**, 1003 (1979).
(5) D. Thienpont, J. Van Cutsem, F. Van Gerven, J. Heeres, and P. A. J. Janssen, *Experientia*, **35**, 606 (1979).
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(7) J. Symoens and G. Cauwenberg, *Prog. Drug. Res.*, in press.

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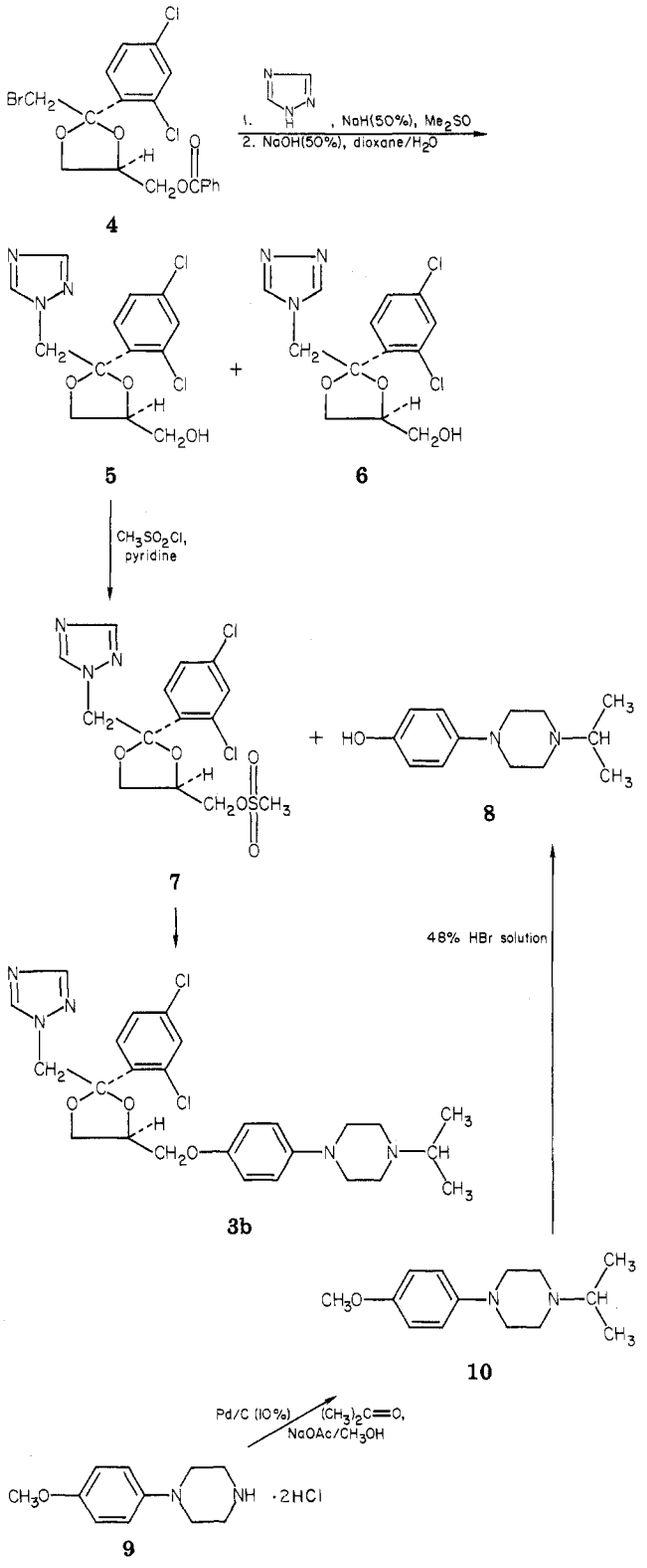
Scheme I



on silica gel. Correct structures were assigned after ^1H NMR spectroscopy. Alcohol **5** is converted to the corresponding methanesulfonate **7**, which is coupled with the sodium salt of phenol **8** to give terconazole **3b**. Starting from 1-(4-methoxyphenyl)piperazine (**9**), phenol **8** is prepared by successive reductive alkylation with acetone and demethylation of the resulting piperazine **10** with 48% HBr solution.

Biological Results

The in vitro results obtained following the method of Godefroi et al.[8] are listed in Table I. Except for *A. fumigatus* and *Mucor* sp. (100 μg/mL), terconazole shows complete or marked inhibition of fungal growth in Sabouraud broth. As for ketoconazole,[9] the in vitro antifungal activity of terconazole largely depends on the test medium. In the presence of 10% inactivated bovine serum, the activity of terconazole was markedly enhanced. Terconazole is also bacteriostatic at 100 μg/mL against *Pseudomonas aeruginosa*, *Erysipelothrix insidiosa*, and *Staphylococcus aureus*.

Bactericidal activity has been observed at 100 μg/mL against *Salmonella pullorum* and *Streptococcus pyogenes* in phenol red dextrose broth. At this concentration, terconazole is devoid of activity against *Escherichia coli*. In vivo topical terconazole (0.5%) and clotrimazole (1%) have been tested therapeutically (treatment starting 3 days after infection) in experimental candidosis in rats, according to the method described by Heeres et al.[4] In guinea pigs, both compounds also have been compared in experimental trichophytosis and microsporosis induced by *T. mentagrophytes* and *M. canis*, respectively, according to the method of Van Cutsem et al.[2]

In experimental vaginal candidosis, 0.5% terconazole b.i.d. for 3 days is equivalent or superior to 1% clotrimazole (Table II). In experimental trichophytosis, treatment for 12 days o.d. with 0.5% terconazole results in complete cure, whereas only 67% of the animals treated with 1% clotrimazole show complete cure or marked improvement (Table II).

In experimental microsporosis, the same treatment period with terconazole and clotrimazole gives response rates of 100 and 63%, respectively. After oral administration, terconazole is less active than ketoconazole in vaginal candidosis, curing at 10 mg/kg only 50% of the infected animals vs. 95% with ketoconazole.[10]

Based on available biological results,[11] it can be expected that terconazole will be effective in topical treatment of superficial fungal infections of different etiology. Terconazole is undergoing clinical evaluation as a topical agent.

Experimental Section

Melting points are measured with a Mettler PF_1 melting point apparatus and are uncorrected. New compounds were routinely checked for their structure by UV and/or IR and NMR spectrometry (UV, Hewlett-Packard HP-8450; IR, Perkin-Elmer 580 B; NMR, Brucker WP 200).

***cis*-2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol (5) and *cis*-2-(2,4-Dichlorophenyl)-2-(4*H*-1,2,4-triazol-4-ylmethyl)-1,3-dioxolane-4-methanol (6).** To a suspension of NaH (50%) (5.3 g, 0.11 mol) dispersion in dry Me_2SO (100 mL) was added triazole (6.9 g, 0.10 mol). After the mixture was stirred for 1 h, 4 (30.0 g, 0.067 mol) was added and stirring at 130 °C was continued overnight. After the mixture was cooled, diluted with water, and extracted with CH_2Cl_2 and the organic extract was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo, an oily residue was obtained, which was dissolved in dioxane (150 mL) and H_2O (30 mL). This solution was refluxed with 200 mL of 50% NaOH in H_2O for 2 h. The reaction mixture was cooled, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo. The oily residue was chromatographed on silica, eluting with $CHCl_3/CH_3OH$ (98:2)

(8) E. F. Godefroi, J. Van Cutsem, C. A. M. Van der Eycken, and P. A. J. Janssen, *J. Med. Chem.*, **10**, 1160 (1967).
(9) J. Van Cutsem, *Am. J. Med.*, in press.
(10) J. Van Cutsem, unpublished results.
(11) J. Van Cutsem, in preparation.

Table I. Complete or Marked Inhibition of Growth at the Concentrations[a] Indicated in Sabouraud Broth after 14 Days of Incubation

	terconazole				clotrimazole
	Sabouraud broth		Sabouraud broth + 10% inact. bovine serum		Sabouraud broth
	inhibition		inhibition		inhibition
organism	complete	marked[b]	complete	marked[b]	complete
Microsporum canis	100	100	100	10	<1
Trichophyton mentagrophytes	1	1	1	0.1	<1
Trychophyton rubrum	100	10	10	1	<1
Cryptococcus neoformans	10	1	1	0.1	>100
Candida albicans	>100	10	100	0.1	>100
Candida tropicalis	10	1	1	0.1	>100
Phialophora verrucosa	100	10	10	1	>100
Sporothrix schenckii	100	100	100	1	>100
Asperigillus fumigatus	>100	>100	>100	100	100
Mucor sp.	>100	>100	100	100	>100
Saprolegnia sp.	100	10	10	1	>100

[a] Concentration in micrograms per milliliter. [b] More than 50% inhibition of growth after 14 days of incubation.

Table II. Therapeutic Topical Treatment of Superficial Mycoses

	terconazole (0.5%)				clotrimazole (1%)		
exptl fungal infection	no. of animals	days of treatment	cured[c]	markedly improved[d]	no. of animals	cured	markedly improved[d]
vaginal candidosis (rats)[a]	48	3 b.i.d.	35	2	10	2	2
trichophytosis (guinea pigs)[b]	20	12 o.d.	20	0	6	3	1
microsporosis(guinea pigs)[b]	36	12 o.d.	19	17	8	4	1

[a] Test compounds were formulated in PEG 200. [b] Test compounds were formulated in a 40:60 mixture of PEG 400 and PEG 1500. [c] Clinical cure with negative microscopy and negative cultures. [d] (a) Presence of some residual lesions with negative microscopy and negative cultures. (b) Absence of clinical lesions but positive microscopy or some positive cultures.

to give **5** [9.3 g (42%); mp 138.2 °C; NMR ($CDCl_3$) δ 7.93 (1 H, s), 8.18 (1 H, s). Anal. ($C_{13}H_{13}Cl_2N_3O_3$) C, H, N] and **6** [0.9 g (4%); mp 180.2 °C; NMR ($CDCl_3$) δ 8.25 (2 H, s). Anal. ($C_{13}H_{13}Cl_2N_3O_3$) N] after crystallization from 4-methyl-2-pentanone/*i*-Pr_2O.

***cis*-[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl Methanesulfonate (7).** To a solution of **5** (6.6 g, 0.02 mol) in dry pyridine (20 mL) was added dropwise methanesulfonyl chloride (2.5 g, 0.022 mol) over a period of 20 min while cooling on ice. The reaction mixture was stirred overnight. The product crystallized on dilution with water. The solid was filtered off and recrystallized from H_2O, yielding **7** (7.1 g, 87%), mp 98.0 °C. Anal. ($C_{14}H_{15}Cl_2N_3O_5S$) C, H, N.

***cis*-1-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine (3b).** To a suspension of NaH (50%) dispersion (0.6 g, 0.012 mol) in oil in Me_2SO (100 mL) was added **8** (2.5 g, 0.01 mol). The mixture was stirred for 1 h, **7** (4.1 g, 0.01 mol) was added, and stirring was continued at 80 °C for 4 h. After cooling, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to leave an oily residue, which solidified on standing. Crystallization from *i*-Pr_2O afforded **3b** (3.4 g, 64%), mp 126.3 °C. Anal. ($C_{26}H_{31}Cl_2N_5O_3$) C, H, N.

4-(4-Methoxyphenyl)-1-(1-methylethyl)piperazine (10). A solution of **9** (13.3 g, 0.05 mol) and acetone (5 mL) in CH_3OH (100 mL) was hydrogenated in the presence of NaOAc (9.0 g, 0.11 mol) with 10% Pd/C (1.0 g) as a catalyst. When hydrogen uptake was complete, the catalyst was filtered off, and the filtrate was evaporated in vacuo. Water was added to the residue, and the mixture was made alkaline with NaOH solution (pH 10). After the mixture was extracted with CH_2Cl_2 and the extract was dried ($MgSO_4$) and evaporated, an oily residue was obtained, which was dissolved in an EtOH/acetone mixture. The product crystallized as the HCl salt by the addition of a small excess of HCl/*i*-PrOH solution. The crystals were filtered off and recrystallized from EtOH, yielding **10** (10.5 g, 68%), mp 230.1 °C. Anal. ($C_{14}H_{22}N_2O$·2HCl) N, Cl.

4-(4-Hydroxyphenyl)-1-(1-methylethyl)piperazine (8). A solution of **10** (9.5 g, 0.031 mol) in 48% HBr solution (100 mL) was refluxed overnight. The reaction mixture was cooled and evaporated in vacuo. The residue was dissolved in H_2O (100 mL), and the solution was neutralized with $NaHCO_3$, whereupon the product crystallized out. The crystalline solid was collected and recrystallized from *n*-BuOH to yield **8** (5.8 g, 85%), mp 274.4 °C. Anal. ($C_{13}H_{20}N_2O$) N.

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Registry No. **3b**, 67915-31-5; **4**, 61397-56-6; **5**, 67914-85-6; **6**, 84499-45-6; **7**, 67914-86-7; **8**, 67914-97-0; **9**, 38869-47-5; **10**, 84499-46-7; **10**·2HCl, 67914-91-4; triazole, 288-88-0.