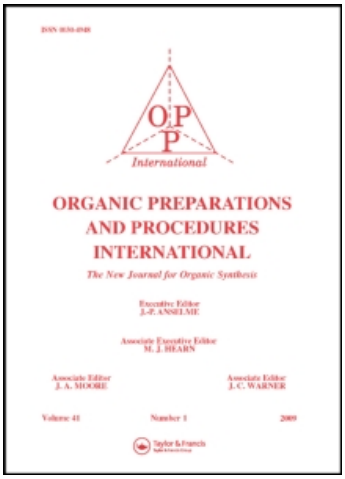

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SYNTHESIS OF 1-(2-(2,4-DICHLOROPHENYL)-2-[(2-THIENYL)METHOXY]ETHYL]-lH-IMIDAZOLE AND 1-[2-(2,4-DICHLOROPHEL)-2-[(2-FURYL)METHOXY]ETHYL]-1H-IMIDAZOLE, TWO NEW MICONAZOLE ANALOGUES

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6. This material was identical (by mp. and spectral features) with an authentic sample (**4a**) as isolated from urine and provided by the Drug Metabolism Unit, The Upjohn Co., Kalamazoo, MI 49001. The two samples were also of identical R_f values (0.61) on TLC; silica gel, heptane-ethanol-chloroform-water (33:33:33:1).

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SYNTHESIS OF 1-[2-(2,4-DICHLOROPHENYL)-2-[(2-THIENYL)METHOXY]ETHYL]-1H-IMIDAZOLE AND 1-[2-(2,4-DICHLOROPHENYL)-2-[(2-FURYL)METHOXY]ETHYL]-1H-IMIDAZOLE, TWO NEW MICONAZOLE ANALOGUES

Submitted by (12/17/91)

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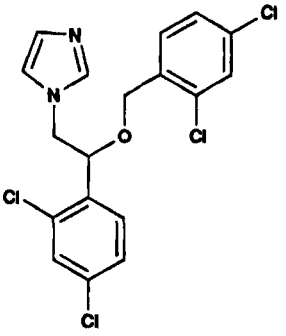
Miconazole (**1**) has a broad-spectrum antifungal activity *in vitro* and its therapeutic use in the treatment of dermatophytic infections is well known.[1] The preparation of **1** and several of its derivatives was described in 1969.[2] The importance of the imidazole nucleus in these compounds was clearly illustrated by the fact that its replacement by other heterocyclic rings generally afforded less



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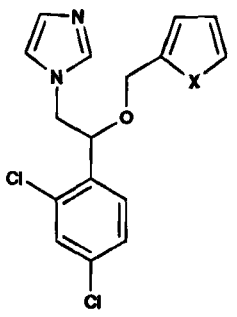
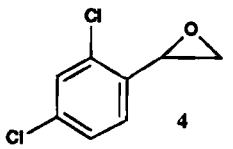


2 X = S
3 X = O



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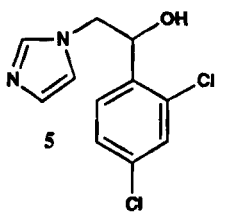

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active or inactive compounds.[3] The present work describes the synthesis of 1-[2-(2,4-dichlorophenyl)-2-[(2-thienyl)methoxy]ethyl]-1-H-imidazole (**2**), and of 1-[2-(2,4-dichlorophenyl)-2-[(2-furyl)-methoxy]ethyl]-1-H-imidazole **3**, two new miconazole analogues. In addition, we report the synthesis of 2,4- dichlorophenyloxirane (**4**), a key intermediate in the synthesis of 1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethanol (**5**), a useful intermediate for the preparation of a large variety of antimicotic agents derived from imidazole.

Compound **4** was formerly considered as not being readily accessible for use in the preparation of miconazole[2] and its analogues. However, recent modifications[4] of the method reported earlier by Corey and Chaykovsky[5] for the transformation of aldehydes into oxiranes has proven useful in the preparation of compound **4**. Epoxide formation is effected by means of sulfur ylide insertion into aldehydes under heterogeneous conditions in the presence of small quantities of water.[6] Under optimum conditions, high yields of epoxides are obtained. Indeed, when commercially available 2,4-dichlorobenzaldehyde was treated at 60° with trimethylsulfonium iodide and potassium hydroxide in acetonitrile containing a small amount of water, epoxide **4** was obtained in 82% yield. Better results could not be obtained when the reaction was carried out with trimethylsulfoxonium iodide under a variety of conditions.

It is well known that under non-acidic conditions, the nucleophilic opening of unsymmetrical oxiranes is governed by the structure of epoxide and the reaction condions.[7] In basic solution, mono-substituted oxiranes are attacked predominantly at the less sterically hindered carbon to yield the most substituted alcohols. Thus epoxide **4** was reacted with imidazole in a 1:1 molar ratio in the presence of pyridine and absolute ethanol under reflux for 12 hrs to produce 1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethanol (**5**) in 63% yield. The syntheses of **1-3** were accomplished by the usual procedure which involved the reaction of the anion **5** with 2,4-dichlorobenzyl chloride, 2-chloromethylthiophene and 2-chloromethylfuran, respectively.

Determination of the biological activity of **2** and **3**, is in progress and will be reported elsewere.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 283-B and Nicolet FT-5S spectrophotometers using chloroform solutions. The ^{1}H NMR spectra were obtained on a Varian FT-80 instrument with TMS as internal standard. The mass spectra were recorded with a Hewlett Packard 5985 B spectrometer with GC/MS system.

2,4-Dichlorophenyloxirane (4).- In a 200 mL, two-necked round-bottom flask equipped with magnetic stirrer, reflux condenser and nitrogen inlet, was placed a mixture of 15 g (85 mmol) of 2,4-dichlorobenzaldehyde, 17.35 g (85 mmol) of trimethylsulfonium iodide,[8] 9.5 g (0.170 mol) of potassium hydroxide, 0.4 mL (23 mmol) of water and 300 mL of acetonitrile. The suspension was stirred under nitrogen at 60° for 3 hrs and after this period the reaction mixture was allowed to cool to room temperature and the resulting solid was filtered off and the filtrate was evaporated. The residue was purified by flash column chromatography on silica (70-230 mesh) and elution with a 8:2 hexane-ethyl

acetate mixture to give 13.3 g (82%) of oxirane **4** as a yellow pale oil. IR ($CHCl_3$): 3062, 2995, 2919, 1594, 1562, 1382, 880 and 825 cm-1; ^1H NMR ($CDCl_3$): δ 2.60 (dd, 1H, J_{AB} = 7 Hz and J_{AX} = 3 Hz, Ha), 3.15 (dd, 1H, J_{BA} = 7 Hz, J_{BX} = 4 Hz, Hb), 4.10 (dd, 1H, J_{XA} = 3 Hz and J_{XB} = 4 Hz, 1Hx), 7.15-7.35 (m, 3H, Ar-H); MS (m/z relative intensites): 188 (20, M^+), 190 (15, $M^+ + 2$), 192 (2, $M^+ + 4$), 158 (29), 153 (61), 125 (51), 123 (100).

Anal. Calcd. for $C_8H_6Cl_2O$: C, 50.83; H, 3.20; Cl, 37.51. Found : C, 50.63; H, 3.31; Cl, 37.70

1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethanol (5).- In a 100 mL, three-necked round bottom flask equipped with an addition funnel, reflux condenser and magnetic stirrer, a solution of 4.4 g (65 mmol) of imidazole in 25 mL of absolute ethanol and 0.15 mL (2 mmol) of dry pyridine was heated at reflux under a nitrogen atmosphere for 30 min. After this time, a solution of 12 g (64 mmol) of oxirane **4** in 10 mL of absolute ethanol was added dropwise and the reaction mixture heated under reflux for 12 hrs. After the reaction was allowed to cool, the ethanol was removed under vacuum, water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over magnesium sulfate and the solvent evaporated. The residue was crystallized from dichloromethane-hexane to afford 9.8 g (63%) of **5** as white crystals, mp 131-132°, lit.[2] 134-135°. IR ($CHCl_3$): 3612, 3118, 3076, 2975, 1590, 1561, 1510, 1469, 1047, 867, 823 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.90 (dd, 1H, J_{AB} = 14 Hz and J_{AX} = 8 Hz, Ha) , 4.20 (dd, 1H, J_{BA} = 14 Hz and J_{BX} = 4 Hz, Hb) , 5.20 (dd, 1H, J_{XA} = 8 Hz and J_{XB} = 4Hz, Hx), 5.80 (s, 1H, -OH) 6.84-7.53 (m, 6H); MS (m/z relative intensites): 256 (3, M^+), 258 (1, $M^+ + 2$), 223 (20), 221 (57), 177 (18), 175 (56), 82 (100), 81 (90).

General Procedures for the Preparation of Miconazole 1-3.- A suspension of 50% sodium hydride dispersed in oil (3.6 g, 75 mmol) washed twice with 10 mL portion of dry hexane in dry tetrahydrofuran (THF, 5 mL) and dry hexamethylphosphoramide (HMPA, 5 mL) under a nitrogen atmosphere was cooled with an ice bath to 4° and a solution of 6 mmol of compound **5** in dry THF (2.5 mL) and HMPA (2.5 mL) was added. The reaction mixture was stirred a RT for 30 min, cooled to 4° and 7 mmol of freshly distilled 2,4-dichlorobenzyl chloride (or 2-chloromethylthiophene[9] or 2-chloromethylfuran[10]) was added; the mixture was heated at 45° for 16 hrs. After this time, the reaction mixture was poured into ice water and extracted with methylene chloride (3 x 15 mL). The extract was dried over anhydrous magnesium sulfate and the solvent evaporated. The residue was purified by column chromatography using silica gel and a mixture of methylene chloride-methanol (90:10) as eluent to afford miconazole **1** in 73% yield, compound **2** in 68% yield and compound **3** in 65% yield respectively.

Miconazole 1: Oil, IR ($CHCl_3$): 3118, 3067, 2968, 1590, 1435, 1285, 1141 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.16 (m, 2H), 4.25 (d, 1H, J = 12 Hz), 4.45 (d, 1H, J = 12 Hz), 4.98 (dd, 1H, J = 3 Hz, J = 4 Hz), 6.93 (m, 2H), 7.28 (m, 6H), 7.48(m, 1H); MS (m/z relative intensities): 414 (2.5, M^+), 416 (3, $M^+ + 2$), 418 (1.6, $M^+ + 4$), 420 (0.4, $M^+ + 6$), 337 (27), 335 (42), 333 (38), 161 (73), 159 (100).

1-(2-(2,4-dichlorophenyl)-2-[(2-thienyl)methoxy]ethyl]-1-H-imidazole (2).- Oil, IR ($CHCl_3$): 3107, 3077, 2936, 2863, 1380, 1344 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.05 (dd, 1H, J = 4 Hz, J = 8 Hz), 4.15 (dd, 1H, J = 3 Hz, J = 8 Hz), 4.35 (d, 1H, J = 12 Hz), 4.60 (d, 1H, J = 12 Hz), 5.00 (dd, 1H, J = 4 Hz, J = 3 Hz), 7.00-7.45 (m, 9H); MS (m/z relative intensities): 352 (0.5 M^+), 354 (0.2 $M^+ + 2$), 178 (9.2), 99

(5.0), 98 (6.1), 97 (100).

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2OS$: C, 54.40; H, 3.99; Cl, 20.10; N, 7.90; S, 9.10
Found: C, 54.61; H, 4.23; Cl, 19.87; N, 7.69; S, 8.76

1-(2-(2,4-dichlorophenyl)-2-[(2-furyl)methoxy]ethyl]-1-H-imidazole (3).- Oil, IR ($CHCl_3$): 3105, 2918, 1570, 1147, 910 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.05 (m, 2H), 4.15 (d, 1H, J = 10 Hz), 4.40 (d, 1H J = 10 Hz), 4.95 (dd, 1H, J = 3 Hz, J = 4 Hz), 6.23 (m, 2H), 6.9 (m, 2H), 7.30 (m, 4H); MS (m/z relative intensities): 336 (2, M^+), 338 (1, $M^+ + 2$), 162 (27), 82 (7), 81 (100), 53 (16).

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O_2$: C, 56.99; H, 4.18; Cl, 21.01; N, 8.31
Found: C, 57.21; H, 4.27; Cl, 20.78; N, 8.16

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