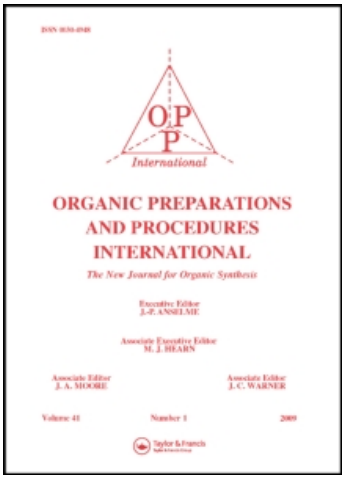


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# SYNTHESIS OF 4-*trans*-[1-[4-[2-(5-CHLORO-2-METHOXYBENZAMIDO)ETHYL] BENZENESULFONYL]UREIDO]CYCLOHEXANOL HEMISUCCINATE ESTER

Robert L. Stephont[a]; R. Sam Niedbala[b]; Keith J. Schrayt[a]; Ned D. Heindel[a]
[a] Department of Chemistry, Lehigh University, Bethlehem, PA [b] STC, Bethlehem, PA

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dichloromethane, dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give **1**. Recrystallization from isopropyl alcohol gave 21.6 g (58%) of pure **1**, mp. 87°, lit.[2] mp. 87-89°.

$^1$H NMR (DMSO-$d_6$): δ 0.9-1.6 (m, 6H, $CH_3$) , 2.5-3.3 (m, 4H, $\underline{CH_2}CH_3$), 4.15 (s, broad, 2H, Ar$\underline{CH_2}$), 7.15 (d, 1H, Ar$\underline{H}$), 8.05 (d, 1H,.Ar$\underline{H}$), 8.45 (d, 1H, Ar$\underline{H}$) ppm.

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## SYNTHESIS OF 4-*trans*-[1-[4-[2-(5-CHLORO-2-METHOXYBENZAMIDO)ETHYL] BENZENESULFONYL]UREIDO]CYCLOHEXANOL HEMISUCCINATE ESTER

*Submitted by* (09/05/91)

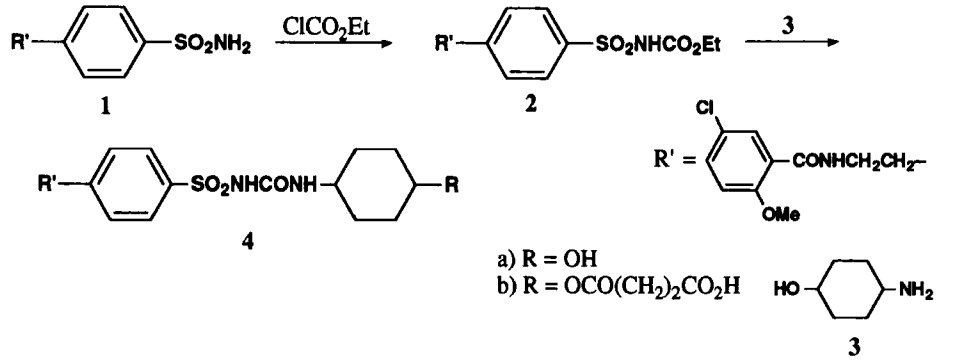
Robert L. Stephon[†], R. Sam Niedbala[††], Keith J. Schray[†], and Ned D. Heindel[†*]

[†] *Department of Chemistry*
*Lehigh University, Bethlehem, PA 18015*

[††] *STC, 115 Research Dr., Bethlehem, PA 18015*

Glyburide (**4**, R = H), 1-[4-[2-(5-chloro-2-methoxybenzamido)ethyl]benzenesulfonyl]-3-cyclohexylurea (**Micronase**, *The Upjohn Company*) is an orally active sulfonylurea drug used in treatment of type II (non-insulin dependent) diabetes mellitus. Assays for glyburide have included spectroscopic methods which lack the requisite sensitivity for detection of this drug in biological fluids.[1] Radioimmunoassay techniques are available for monitoring of the drug in plasma, using antisera raised to synthetic derivatives of the parent compound. The compound used to develop the existing radioimmunoassay contained a 4-acetic acid moiety as the attachment arm (**4**, R = $CH_2COOH$).[2] Synthesis of that target was accomplished by condensation of methyl 4-(isocyanato)cyclohexylacetate

with **1**. This reaction scheme was pioneered by Hsi who also employed **1** (bearing either a $^{14}C$ or a $^{3}H$)




with cyclohexylisocyanate to prepare a radiotracer version of glyburide[3] by the very process used commercially in the synthesis of the parent drug.[4]

An improved approach to glyburide analysis would involve the use of less invasive (urine) specimens containing the metabolite of (**4**, R = H) in a safer, more economical non-isotopic immunoassay.[5] The sensitivity and specificity of an immunoassay for the metabolite may be increased by use of an antigen **4a** that most closely resembles this structure. This requires an analogue that contains the metabolite structure which is functionalized, conjugated to protein, and used to elicit the appropriate antibodies. A synthetic route to **4a** is unavailable in the literature and would be obviously preferable to the present process of isolating this metabolite from urine. We report herein not only the synthesis of the metabolite, but also its linkable hemisuccinate **4b**. The former (**4a**), prepared from a 4-aminocyclohexanol (**3**) and a carbamate (**2**), eschews the use of an isocyanate in order to avoid competing reactivities. The latter (**4b**) is readily prepared from **4a** and succinyl chloride.



## EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns apparatus and are reported uncorrected. IR spectra were obtained on Perkin Elmer 1420 spectrophotometer. NMR spectra were obtained on a JEOL FX90Q, and FAB MS on a Kratos 83 instrument.

**Ethyl 4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonamidecarbamate (2).**- To a mixture of the known sulfonamide (**1**)[4] (5.00 g, 13.6 mmol) and anhydrous potassium carbonate (4.89 g, 35.4 mmol) in 300 mL of reagent acetone was added, over 3 hrs with stirring, 1.7 mL (18 mmol) of ethyl chloroformate. The mixture was stirred and refluxed for 48 hrs, allowed to cool to room temperature, and filtered. The resulting potassium salt of (**2**) was dissolved in a minimum of water (1 liter), and any insoluble material was removed by filtration. The solution was acidified by the dropwise addition of concentrated hydrochloric acid, and the product precipitated. The crude product was recrystallized from 95% ethanol to yield 3.5 g (58%) of white crystals, mp. 154-155°. IR (KBr): 3385 (NH), 1735 (-COCONH-), 1635 (-CONH-) and 1535 $cm^{-1}$ (-CNH-); $^{1}H$ NMR (DMSO-$d_6$): δ 1.10 (t,

3H, $CH_3$, $J$ = 8 Hz), 2.95 (t, 2H, $CH_2$, $J$ = 6 Hz), 3.55 (t, 3H, $CH_2$ and N-H, $J$ = 6 Hz), 3.82 (s, 3H, $CH_3O$), 4.05 (q, 2H, $CH_2$, $J$ = 8 Hz), 7.02-8.05 (m, 7H, Ar-H), and 8.32 ppm (br t, 1H, NH).

*Anal.* Calcd for $C_{19}H_{21}ClN_2O_6S$: C, 51.76; H, 4.77; N, 6.36. Found: C, 51.28; H, 4.76; N, 6.18

**4-*trans*-[1-[4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonyl]-ureido]cyclohexanol (4a).**- *trans*-4-Aminocyclohexanol hydrochloride (Aldrich) was converted to its free base and isolated by continuous extraction of a basic aqueous solution (10% aqueous NaOH) with diethyl ether. To a solution of the ethyl N-arylsulfonylcarbamate (2) (1.00 g, 2.28 mmol) in 50 mL of toluene was added, during 1 hr with stirring, a solution of the amine (0.30 g, 2.5 mmol) in 10 mL of toluene. The mixture was stirred and refluxed for 3 hrs and cooled to room temperature. The toluene was removed under reduced pressure, and the product recrystallized from 95% ethanol to give 0.78 g (67%) of white solid, mp. 174-175°. IR (KBr): 3400 (OH) and 1720 and 1650 $cm^{-1}$ (urea HNCO carboxamide I and II bands); $^1H$ NMR (DMSO-$d_6$): δ 1.00-1.50 and 1.60-1.95 (m, 8H, cyclohexyl-H), 2.95 (t, 2H, $CH_2$, $J$ = 6 Hz), 3.42 (m, 4H, CH-O, CH-N, 2 N-H), 3.55 (t, 2H, $CH_2$, $J$ = 6 Hz), 3.80 (s, 3H, $CH_3O$), 7.00-8.00 (m, 7H, Ar-H) and 8.33 ppm (t, 1H, N-H, $J$ = 4 Hz). FAB MS in 3-nitrobenzyl alcohol matrix gave a parent ion of 510.14 which was computationally optimized to the expected formula $C_{23}H_{28}ClN_3O_6S$.[6]

*Anal.* Calcd for $C_{23}H_{28}ClN_3O_6S$: C, 54.17; H, 5.53; N, 8.24. Found: C, 54.22; H, 5.40; N, 7.94

**4-*trans*-[1-[4-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonyl]-ureido]cyclohexanol Hemisuccinate Ester (4b).**- To a mixture of 4-hydroxyglyburide (4a) (0.50 g, 0.98 mmol) and succinyl chloride (0.12 mL, 1.1 mmol) in 10 mL of warm anhydrous DMF was added over 0.5 hr with stirring, a solution of pyridine (0.080 mL, 1.0 mmol) in 2 mL of DMF. The solution was stirred for 4 hrs and the reaction mixture added, dropwise with stirring, to 10 mL of a saturated aqueous sodium bicarbonate solution chilled in an ice bath. After 0.5 hr, the liberation of $CO_2$ ceased and the pH was adjusted to 5 with conc. hydrochloric acid. The product was collected, washed with cold water, and recrystallized from 95% ethanol to afford 0.33 g (55%) of an off-white solid, mp. 199-200°. IR (KBr): 3400 (NH), 1750 (-$OCOCH_2$-), 1725, 1710, 1655 (-COOH, and urea HNCO carboxamide I and II bands) and 1545 $cm^{-1}$ (-CHN-); $^1H$ NMR (DMSO-$d_6$): δ 1.20-1.50 and 1.62-2.05 (m, 8H, cyclohexyl-H), 2.83-3.73 (overlapping m, 12H, 4 x $CH_2$'s, CH-O, CH-N, and 2 N-H), 4.01 (s, 3H, $CH_3O$), 7.30-8.22 (m, 7H, Ar-H) and 8.55 ppm (br m, 1H, N-H, $J$ = 4 Hz).

*Anal.* Calcd for $C_{27}H_{32}ClN_3O_9S$ 0.5 $H_2O$: C, 52.38; H, 5.37; N, 6.79

Found: C, 52.03; H, 5.31; N, 6.87

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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

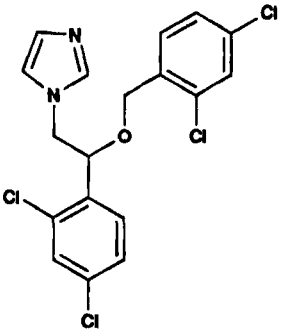
*Submitted by* (12/17/91)

Raymundo Cruz-Almanza*†, Teresa Hernández†, Francisco Pérez† and Cristina Lemini††

† *Instituto de Química*
†† *Departamento de Farmacología, Facultad de Medicina*
*Universidad Nacional Autónoma de México, Circuito Exterior*
*Ciudad Universitaria, México, D. F. 04510, MEXICO*



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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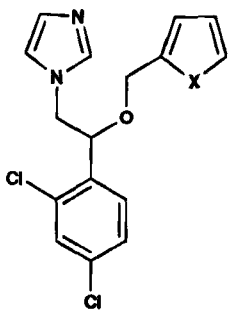
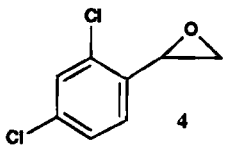


**2** X = S
**3** X = O



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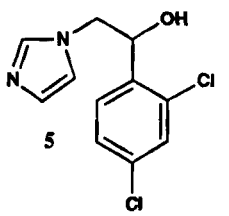

**5**