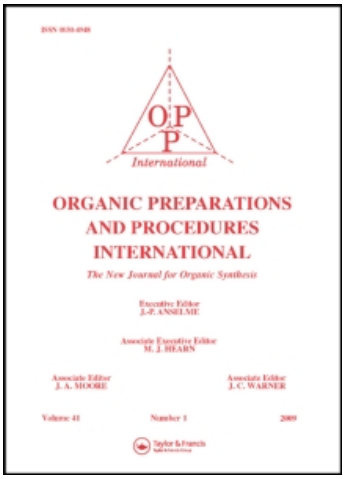


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT SYNTHESIS OF N-[2-[[[5-[(DIMETHYLAMINO)METHYL]-2-FURANYLMETHYL]THIO]ETHYL]THIENO-[3,4-d]ISOTHIAZOL-3-AMINE-1,1-DIOXIDE HYDROCHLORIDE, A POTENT GASTRIC ACID ANTISECRETORY AGENT

Arthur A. Santilli[a]; Robert L. Morris[ab]; Anthony C. Scotese[ab]; Donald P. Strike[a]
[a] Department of Chemistry, Wyeth-Ayerst Research, Princeton, NJ [b] Rorer Central Research, King of Prussia, PA

To cite this Article Santilli, Arthur A. , Morris, Robert L. , Scotese, Anthony C. and Strike, Donald P.(1990) 'A CONVENIENT SYNTHESIS OF N-[2-[[[5-[(DIMETHYLAMINO)METHYL]-2-FURANYLMETHYL]THIO]ETHYL]THIENO-[3,4-d]ISOTHIAZOL-3-AMINE-1,1-DIOXIDE HYDROCHLORIDE, A POTENT GASTRIC ACID ANTISECRETORY AGENT', Organic Preparations and Procedures International, 22: 1, 71 — 76
To link to this Article: DOI: 10.1080/00304949009356668
URL: http://dx.doi.org/10.1080/00304949009356668

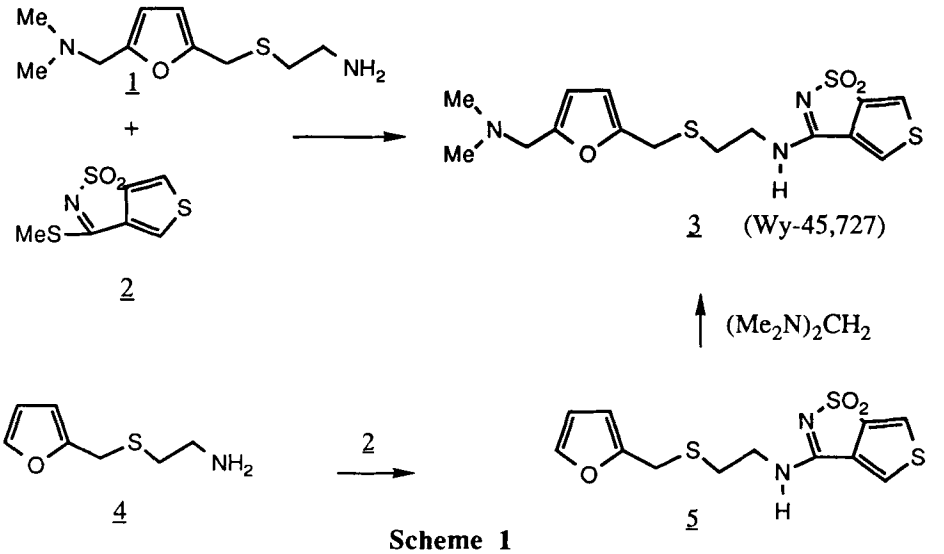
ORGANIC PREPARATIONS AND PROCEDURES INT. 22(1), 71-76 (1990)

A CONVENIENT SYNTHESIS OF N-[2-[[[5-[(DIMETHYLAMINO)METHYL]-2-FURANYLMETHYL]THIO]ETHYL]THIENO-[3,4-d]ISOTHIAZOL-3-AMINE-1,1-DIOXIDE HYDROCHLORIDE, A POTENT GASTRIC ACID ANTISECRETORY AGENT

Arthur A. Santilli*, Robert L. Morris†, Anthony C. Scotese† and Donald P. Strike

Wyeth-Ayerst Research, Department of Chemistry, Princeton, NJ 08543-8000

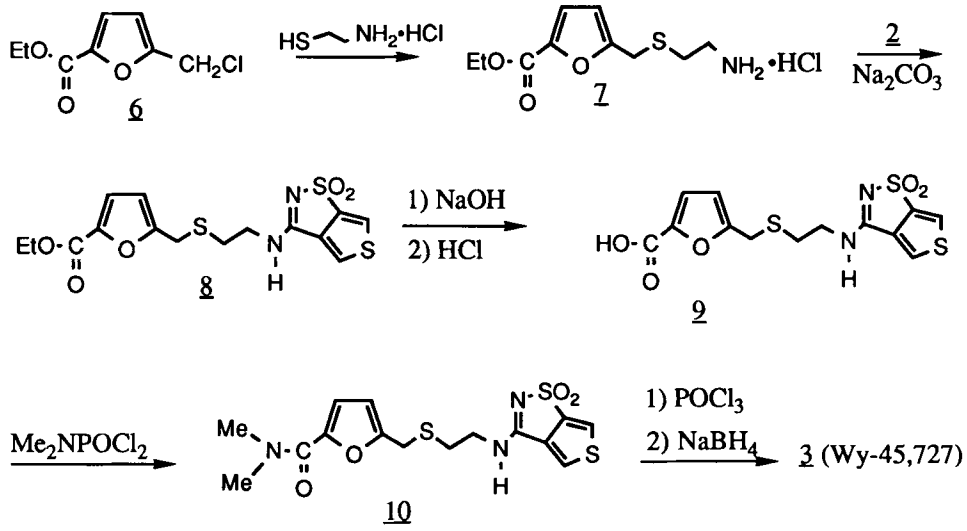
Previously we reported the synthesis and antisecretory activity of N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl] methyl] thio] ethyl] thieno[3,4-d]isothiazol-3- amine- 1, 1-dioxide hydrochloride[1] (3, Wy-45,727) (Scheme 1). The drug has been shown clinically to significantly reduce gastric acid secretion in man,[2-5] a condition of prime importance for efficacious gastric and duodenal ulcer healing. Moreover, the gastric acid antisecretory activity of the drug, an H_2-receptor antagonist, was shown to have significantly greater potency over ranitidine or cimetidine in both the rat and dog pharmacological models.[1]



Scheme 1

During the initial phases of development of 3, 2-[[[5-(dimethylamino)-methyl-2-furanyl]-methyl]thio]ethanamine (1) was used to displace the thiomethyl group in 3-(methylthio)thieno-[3,4-d]isothiazole 1,1-dioxide (2)[6]. The use of 1 has two disadvantages. The amine is thermally unstable[7] and also is restricted from general commercial use by patent.[6] We have previously published an alternative route to 3 (Scheme 1) which avoids these encumbrances by employing 2-[2-(furanylmethyl)thio]ethanamine (4) a more stable amine intermediate which is currently in the public domain.[1] Unfortunately, the preparation of 4 involves the use of furfuryl mercaptan, a compound with a severely noxious stench. We now describe an alternative synthetic pathway to 3 which obviates all of these disadvantages.

The new approach (Scheme 2) starts with the alkylation of 2-aminoethanethiol hydrochloride with ethyl 5-chloromethyl-2-furoate(6) in ethanol to afford 5-[[(2-aminoethyl)thio]-methyl]-2-furancarboxylic acid ethyl ester, isolated as the hydrochloride 7 in 79% yield. Displacement of the thiomethyl group in 2 by one equivalent of 7 in refluxing ethanol in the presence of sodium carbonate gave 5[[[2-(thieno[3,4-d]isothiazol-3-ylamino)ethyl]-thio]-methyl]-2-furancarboxylic acid ethyl ester 1,1-dioxide (8) in 96% yield. The ester was converted to the corresponding carboxylic acid 9 in 64% yield by alkaline hydrolysis using 5% aqueous sodium hydroxide solution followed by acidification. Conversion of 9 to the corresponding N,N-dimethyl carboxamide 10 in 87% yield was achieved by heating 9 with an excess of N,N-dimethylphosphoramidodichloridate in refluxing 1,2-dimethoxyethane. Previous attempts to form this carboxamide by treatment of the ester 8 with dimethylamine under a variety of conditions were unsuccessful. Liu and co-workers have described the use of N,N-dimethylphosphoramidodichloridate as a useful reagent for converting a carboxylic acid to the corresponding N,N-dimethyl carboxamide under mild conditions.[8] They indicate that the reagent has a dual purpose - activation of the carboxyl group by formation of a mixed anhydride and the delivery of the dimethylamino moiety to the carbonyl center. The carbonyl group of the amide was successfully converted to a methylene group by first treating the amide with phosphoryl chloride followed by reduction of the resulting adduct with sodium borohydride in 1,2-dimethoxyethane. The product 3 isolated as a hydrochloride salt was



Scheme 2

identical in all respects with the hydrochloride salt of the product prepared from the reaction of 1 with 2. The present synthesis of 3 utilizes a stable, non-patent restricted amine as a starting material which can be generated from non-foul smelling intermediates.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. ^{1}H-NMR spectra were recorded either on a Varian FT-80A or an XL-100 instrument. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. Coupling constants (J values) are in Hertz (Hz). Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Infrared spectra (IR) were recorded with a Perkin-Elmer Model 299 spectrometer and values are in cm^{-1}. Elemental analyses were performed on a Perkin-Elmer Model 240-elemental analyzer. Yields have not been optimized.

5-[[(2-Aminoethyl)thio]methyl]-2-furancarboxylic Acid Ethyl Ester Hydrochloride (7).- To a mixture of 52.6 g (0.28 mole) of ethyl 5-chloromethyl-2-furoate (6) and 31.7 g (0.28 mole) of 2-aminoethanethiol hydrochloride in 500 mL of EtOH was added 29.5 g (0.28 mole) of $NaHCO_3$. The reaction mixture was stirred under reflux overnight, filtered and the filtrate was evaporated to dryness. Approximately 100 mL of Et_2O was added to the stirred residue. The precipitate which slowly formed was collected on a suction filter and was rinsed with Et_2O. EtOH-HCl (g) was added to the ethereal filtrate and caused

the deposition of more product. The combined crops amounted to 59 g (79% yield). Recrystallization from CH_3CN gave 45 g (60%) of pure product, mp. 140-144 °. IR (KBr): 2930, 1705. ^{1}H-NMR (DMSO-d_6): δ 8.30 (s, 3H), 7.48 (d, 1H, J = 4), 6.63 (d, 1H), 4.25 (q, 2H, J = 7), 3.95 (s, 2H), 2.87 (m, 4H), 1.29 (t, 3H).

Anal. Calcd. for $C_{10}H_{16}ClNO_3S$: C, 45.19; H, 6.07; N, 5.27

Found: C, 44.99; H, 5.88; N, 5.34

5-[[[2-(Thieno[3,4-d]isothiazol-3-ylamino)ethyl]thio]methyl]-2-furancarboxylic Acid Ethyl Ester 1,1-dioxide (8).- A solution of 9.7 g (0.036 mole) of 7 in 150 mL of EtOH was added to a solution of 8.0 g (0.036 mole) of 2[9] in 150 mL of EtOH. Na_2CO_3 (3.8 g, 0.036 mole) was added and the mixture was stirred and heated overnight under reflux. The reaction mixture was filtered and the residue was triturated with a few mL of EtOH. The crystalline product was collected on a filter giving 14.7 g (96% yield). An analytical sample (mp. 136-139°) was obtained by recrystallization of a sample from AcOEt. IR (KBr): 3330, 1720, 1300, 1130. ^{1}H-NMR (DMSO-d_6): δ 9.43 (t, 1H, J = 6.0), 8.39 (dd, 2H, J = 2.5), 7.21 (d, 1H, J = 4.0), 6.58 (d, 1H), 4.32 (q, 2H; J = 6.0), 3.92 (s, 2H), 3.55 (q, 2H, J = 6.0), 2.81 (t, 2H), 1.3 (t, 3H).

Anal. Calcd. for $C_{15}H_{16}N_2O_5S_3$: C, 44.98; H, 4.03; N, 7.00

Found: C, 45.35; H, 4.03; N, 6.97

5-[[[2-(Thieno[3,4-d]isothiazol-3-ylamino)ethyl]thio]methyl]-2-furancarboxylic Acid 1,1-dioxide (9).- A suspension of 8 (4.0 g, 0.01 mole) in 120 mL of 5% NaOH solution was stirred at ambient temperature for 1.5 hr. The reaction mixture was filtered and the filtrate was cooled in ice and then acidified with concentrated HCl. The resulting precipitate was collected and rinsed with H_2O. Recrystallization of the crude product from EtOH gave 2.4 g (64%) of product, mp. 198-200°. IR (KBr): 3300, 2550, 1680, 1280, 1120. ^{1}H-NMR (DMSO-d_6): δ 13.1 (s, 1H), 9.45 (t, 1H, J = 5.0), 8.40 (dd, 2H, J = 2.0), 7.30 (d, 1H,, J = 4.0), 6.50 (d, 1H), 3.87 (s, 2H), 3.09 (q, 2H, J = 6.0), 2.75 (t, 2H, J = 6.0).

Anal. Calcd. for $C_{13}H_{12}N_2O_5S_3$: C, 41.92; H, 3.25; N, 7.52

Found: C, 41.80; H, 3.29; N, 7.68

N,N-Dimethyl-5-[[[2-(thieno[3,4-d]isothiazol-3-ylamino)ethyl]thio]-methyl]-2-furancarboxamide 1,1-dioxide (10).- To a solution of 0.5 g (0.0013 mole) of 9 in 15 mL of 1,2-dimethoxyethane was added 1.6 mL (0.0013 mole) of N,N-dimethylphosphoramidodichloridate. The mixture was heated under reflux for 24 hr while continuously purging the reaction with N_2. After the reaction was allowed to reach room temperature, the dimethoxyethane solution was decanted leaving a gray solid product. The product was triturated with ethanol and collected on a filter. The filtrate was slurried in water and again filtered. The combined precipitates after recrystallization from 2-ethoxyethanol amounted to 0.45 g (87% yield), mp. 220-222°. IR (KBr): 3270, 1615, 1295, 1140. ^{1}H-NMR (DMSO-d_6): δ 9.58 (t, 1H, J = 6.0), 8.2 (s, 2H), 6.90 (d, 1H, J = 4.0), 6.45 (d, 1H), 3.9 (s, 2H), 3.65 (q, 2H, J = 6.0), 3.15 (s, 6H), 2.78 (t, 2H).

Anal. Calcd. for $C_{15}H_{17}N_3O_4S_3$: C, 45.09; H, 4.29; N, 10.52

Found: C, 45.15; H, 4.31; N, 10.60

N-[2-[[[5-[(Dimethylamino)methyl]2-furanyl]methyl]thio]ethyl]-thieno[3,4-d]isothiazol-3-amine 1,1-dioxide, Hydrochloride (3).- To 25 mL of $POCl_3$ was added 0.45 g (0.0011 mole) of 10. The mixture was stirred with gentle heating until a solution was achieved. The reaction mixture was then cooled in ice and evaporated to dryness at ambient temperature using a high vacuum pump. To the residue was added 20 mL of 1,2-dimethoxyethane and the solution was cooled in ice. Sodium borohydride (0.15 g, 0.004 mole) was added to the solution and the reaction was stirred and allowed to warm to room temperature. After 1 hr the reaction mixture was cooled in ice and 10 mL of 10% HCl was added dropwise. The mixture was evaporated at room temperature under vacuum. Water (20 mL) was added to the residue and the mixture was heated under reflux for 20 min. and was then filtered. The filtrate was made basic with 20% Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ phase was dried over $MgSO_4$ and evaporated to dryness giving 0.16 g of crude product as the free base. Purification was achieved by passing a methanol solution of the base through a silica gel 60 column giving 0.08 g of pure free base. The product was dissolved in a few mL of EtOH and EtOH-HCl (g) was added (to pH 1). Chilling and scratching in ice caused precipitation of the hydrochloride salt, mp. 186-188°. (.07 g, 15%

yield). IR (KBr) 3310, 2500, 1280, 1123. The IR and NMR spectra of this material are identical with that of Wy-45,727 prepared via the reaction of 1 with 2 (see reference 1).

Anal. Calcd. for $C_{15}H_{20}ClN_3O_3S_3$: C, 42.69; H, 4.78; N, 9.96

Found: C, 42.91; H, 4.79; N, 9.97

Acknowledgements- We thank Mrs. M. Politowski and staff for the combustion analyses, Mr. B. Hofmann for help with interpreting the ^{1}H-NMR spectra, Mrs. M. Winkler and C. Delfino for typing the manuscript.

REFERENCES

† Present address: Rorer Central Research, King of Prussia, PA 19406.

1. A. A. Santilli, A. C. Scotese, R. L. Morris, S. T. Nielsen and D. P. Strike, Eur. J. Med. Chem., 24, 87 (1989).

2. K. C. Su, G. VanDeventer, T. J. Reedy, B. Sytnik, V. Maxwell and J. H. Walsh, Gastroenterology, 92, 1658 (1987).

3. M. L. Allen, W. C. Orr, M.G. Robinson, M. Silverman and M. Gurwith, ibid., 92, 1294 (1987).

4. H. Merki, L. Witzel, J. Neumann, D. Kaufmann, J. Roehmel, M. Langman and R. Walt, ibid., 92, 1531 (1987).

5. H. S. Merki, D. Kaufmann, M. Kempf, A. Mappes, J. Heim, J. Roehmel and R. Walt, Br. J. Clin. Pharmacol., 27, 135 (1989).

6. B. J. Price, J. W. Clitherow, and J. Bradshaw, U. S. Patent, 4,128,658.

7. T. Laird, Chem. Ind. (London),134 (1978).

8. J. J. Ling, W.H. Chan and S. P. Lee, Synth. Commun., 9 (1), 31 (1979).

9. A. A. Santilli, A. C. Scotese, R. L. Morris, G. A. Schiehser, D. M. Teller, S. T. Nielsen and D. P. Strike, J. Med. Chem., 31, 1480 (1988).

(Received June 30, 1989; in revised form October 23, 1989)