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SYNTHESIS AND CHARACTERIZATION OF A NOVEL RANITIDINE DIMER

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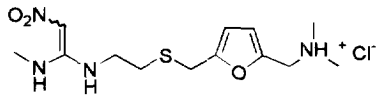
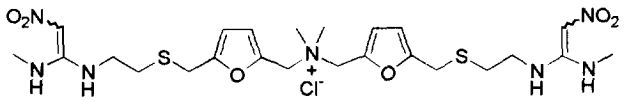
Abstract: A route towards the synthesis of a ranitidine bulk drug product impurity is described. This protocol involves acetyl chloride initiated oxonium ion generation and subsequent trapping to form the corresponding ranitidine dimer (**1**). This synthesis allowed for structure verification of the impurity and provided reference supplies for further analytical and toxicology investigations. © 1997 Elsevier Science Ltd.

Glaxo–Wellcome's H_2-antagonist ranitidine hydrochloride (Zantac™) has been a popular treatment for gastric and peptic ulcers and has recently been approved for over-the-counter use in the United States.[1] Ranitidine hydrochloride has been isolated as a polymorphic crystalline substance with at least two major crystal forms.[2] The patent covering crystal form-one has recently expired. Thus, this pharmaceutical agent is now a target for the generic market.

As part of a program to supply generic ranitidine form-one, quantities of the material were prepared in our manufacturing facility. HPLC analysis of initial bulk drug lots indicated the presence of an early eluting impurity in various concentrations from lot to lot. Subsequent investigation revealed that this material was being formed during an early step in the process. This impurity was isolated and proposed to be the dimeric quaternary salt **1**. As a result of this, it became necessary to prepare multigram quantities of **1** for structure verification and for use as an analytical reference standard. Initial attempts at isolating multigram quantities of **1** from bulk drug lots or seed crystals failed so an effort towards the total synthesis of the proposed dimer **1** was initiated.



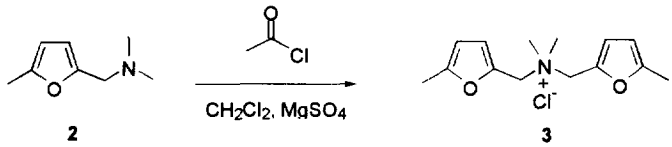
Ranitidine Hydrochloride (Zantac)



Ranitidine Dimer (**1**)

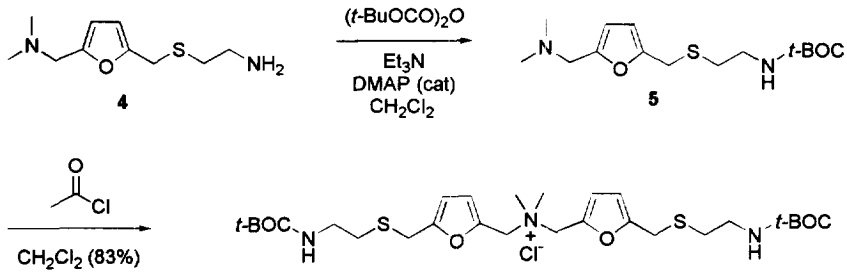
Early efforts towards the synthesis of **1** focused on its direct preparation from ranitidine free base. Treatment of ranitidine free base with ethanol/HCl resulted in the recovery of the corresponding salt with no detectable dimer. In addition, complex mixtures of products were obtained when solutions of the free base or the hydrochloride salt were allowed to stand over magnesium sulfate in dichloromethane.

After this unsuccessful approach, a literature search revealed that the formation of quaternary ammonium salts from *N,N*-dimethylaminomethylfurans was a known process. During a study of Mannich reactions of alkyl furans with imines, Heaney and coworkers[3] observed the spontaneous formation of salt **3** from 2-*N,N*-dimethylaminomethyl-5-methylfuran (**2**) when solutions of **2** in dichloromethane were allowed to stand for several days over magnesium sulfate. Moreover, Heaney reported the quantitative formation of quaternary salt **3** upon treatment of **2** with 0.5 equivalents of acetyl chloride (eq 1).



2 **3** (1)

Consideration of Heaney's results led to the dimerization shown in equation 2. The thiodiaminofuran (**4**) was prepared following the Glaxo protocol[4] and subsequently protected as the *N*-BOC derivative **5**.[5]

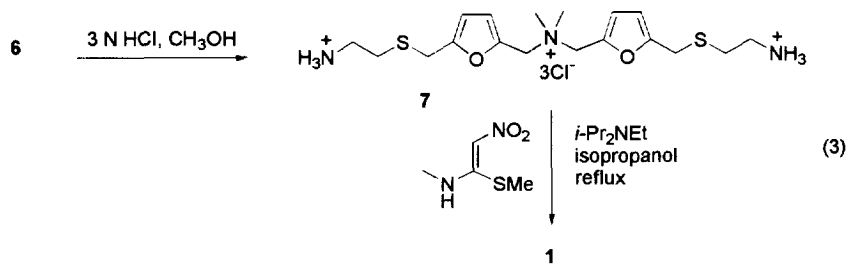


4 **5** (2)

6

Treatment of **5** with acetyl chloride effectively furnished the desired BOC-protected dimer in high yield after chromatography.

Deprotection of **6**[6] with aqueous HCl in methanol provided salt **7**[7] (eq 3), which in turn was coupled with *N*-methyl-1-(methylthio)-2-nitroethenamine to afford the desired dimeric product **1**[8] in an unoptimized 55% yield.



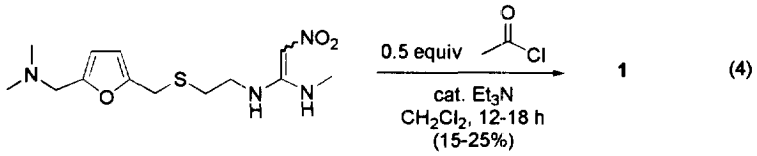
7 (3)

1

Crude ^{1}H NMR spectra of the transformation of **7** to **1** indicated that the reaction was clean and efficient. The moderate yield can be accounted for through losses encountered during chromatographic purification on silica gel.

With modest amounts of **1** in hand, it was now possible to fully characterize it and demonstrate that it was indeed the proposed structure.

In order to streamline this protocol, a direct synthesis of **1** from ranitidine free base **4** was attempted (eq 4). Treatment of the free base with acetyl chloride and a catalytic amount of triethylamine resulted in the formation of **1**[9] in modest yield (15 to 25%) after chromatography on neutral alumina. Analysis of the crude mixture showed that the two major components were **1** and unreacted ranitidine.



Through the use of an acetyl chloride initiated oxonium ion[10] we have been able to prepare multigram quantities of a bulk drug product impurity. Although the overall yield is modest, there is potential for improvement since the losses occur during chromatographic purification of the quaternary ammonium salt dimer on conventional supports. The preparation of **1** allowed for structure verification and furnished supplies for a variety of studies. In addition, this investigation has given valuable insight on the origin of the dimer in our production lots.

Acknowledgements

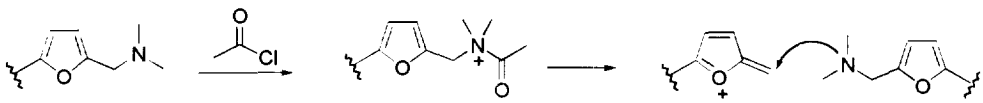
The authors wish to thank BI Chemicals, Petersburg VA, for the generous supply of ranitidine free base and hydrochloride salt and the Analytical Department at Boehringer Ingelheim for support and analytical data.

References and Notes

1. For a general description see: Hillier, K. *Drugs of the Future* **1979**, Vol. IV, 9, 663; Daly, M. J.; Price, B. J. *Prog. Med. Chem.* **1983**, *20*, 337.
2. Madan, T.; Kakkar, A. P. *Drug Dev. Ind. Pharm.* **1994**, *20*, 1571; Crookes, D. L. US Patent 4,672,133, **1987**; Crookes, D. L. FR Patent 2491067, **1982**; *Chem. Abstr.* **1982**, *97*, 61014.
3. Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron Lett.* **1988**, *29*, 2377.
4. Price, B. J.; Clitherow, J. W.; Bradshaw, J. US Patent 4,128,658, **1978**; *Chem. Abstr.* **1978**, *88*, 190580.
5. **Compound 5:** A solution of di-*tert*-butyl dicarbonate (3.78 g, 17.4 mmol) and dichloromethane (5 mL) was added dropwise to a stirred solution of **4** (1.51g, 7.04 mmol), triethylamine (1.20 mL, 8.61 mmol), DMAP (22.0 mg, 0.18 mmol) and dichloromethane (35 mL) at room temperature. The resulting solution was stirred at room temperature for 12 h. Aqueous workup (aqueous $NaHCO_3$, dichloromethane, Na_2SO_4) afforded crude **5** as a brown oil. Flash chromatography (silica gel, 9:1 ethyl acetate/methanol) afforded 1.10 g (50%) of pure **5** as a yellow oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.10 (s, 2H), 3.70 (s, 2H), 3.40 (s, 2H), 3.21 (q, J = 6.3 Hz, 2H), 2.60 (t, J = 6.6 Hz, 2H), 2.23 (s, 6H), 1.43 (s, 9H).
6. **Quaternary ammonium salt 6:** Acetyl chloride (119 μL, 1.46 mmol) was added dropwise to a stirred solution of **5** (830 mg, 2.64 mmol) and dichloromethane (17 mL) at room temperature. The mixture was

stirred at room temperature for 12 h. Aqueous workup (aqueous $NaHCO_3$, dichloromethane, brine, Na_2SO_4) afforded a yellow oil. Flash chromatography (neutral alumina, 4:1 ether/methanol), followed by trituration with dichloromethane, afforded 680 mg (83%) of pure **6** as a yellow solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.89 (d, J = 3.2 Hz, 2H), 6.28 (d, J = 3.2 Hz, 2H), 5.01 (br, 6H), 3.69 (s, 4H), 3.25 (obscured q, 4H), 3.23 (s, 6H), 2.59 (t, J = 7.0 Hz, 4H), 1.39 (s, 18 H); MS (ion spray) *m/z* 584 (M^+, 100).

7. **Quaternary ammonium salt 7:** Hydrochloric acid (300 μL of a 3 N solution) was added to a stirred solution of **6** (103 mg, 0.166 mmol) and methanol (2 mL) at room temperature. The mixture was stirred at room temperature for 12 h and concentrated under reduced pressure to afford 7 as a dark brown oil: ^{1}H NMR (270 MHz, d_6-DMSO) δ 8.02 (br, 6H), 6.84 (d, J = 3.2 Hz, 2H), 6.49 (d, J = 3.2 Hz, 2H), 4 60 (s, 4H), 3.89 (s, 4H), 3.01 (q, J = 6.4 Hz, 4H), 2.93 (s, 6H), 2.70 (t, J = 7.4 Hz, 4H).
8. **Preparation of Dimer 1 from 7:** *N*-methyl-1-(methylthio)-2-nitroethenamine (754 mg, 5.09 mmol) was added to a stirred solution of crude salt **7** (1.81 mmol), diisopropylethylamine (1.6 mL, 9.18 mmol) and isopropanol (18 mL) at room temperature. The mixture was then refluxed for 18 h and concentrated under reduced pressure to afford a dark oil. Flash chromatography (neutral alumina, 3:1 ethyl acetate/methanol) afforded 614 mg (55%) of **1** as an amorphous yellow solid.
9. **Direct synthesis of ranitidine dimer 1**: Acetyl chloride (110 μL, 1.46 mmol) was added dropwise to a stirred solution of ranitidine free base (1.0g, 2.85 mmol), triethylamine (100 μL, 0.717 mmol) and dichloromethane (9.5 mL) at room temperature. The mixture was stirred for 12 h and allowed to settle for 3 h. The solvent was decanted and placed in a different flask while the dark brown precipitate obtained was set aside. Acetyl chloride (20 μL) was added to the dichloromethane solution containing unreacted ranitidine and the resulting mixture was stirred for 12 h then allowed to settle for 3 h. The dark oil precipitate was removed from the solvent portion and combined with the precipitate collected earlier. The resulting oil was purified twice by flash chromatography (neutral alumina, ethyl acetate/methanol, 4:1-2:1 $^v/_v$), triturated with dichloromethane to afford 216 mg (25%) of product as a pale yellow solid: mp 102-111 °C: ^{1}H NMR (270 MHz, d_4-methanol) δ 6.84 (d, J = 3.2 Hz, 2H), 6.67 (s, 2H), 6.43 (d, J = 3.2 Hz, 2H), 4.56 (s, 4H), 3.86 (s, 4H), 3.41 (t, J = 6.5 Hz, 4H), 3.00 (s, 6H), 2.86 (s, 6H), 2.79 (br t, J = 6.5 Hz, 4H); ^{13}C NMR (67.5 MHz, d_4-methanol) δ 158.0, 157.2, 143.7, 119.5, 110.7, 99.4, 60.8, 31.8, 28.7; MS (ion spray) *m/z* 584 (M^+, 37), 315 (100); Anal. calcd for $C_{24}H_{38}ClN_7O_6S_2$-$^1/_2$ H_2O: C, 45.82; H, 6.25; N, 15.58; Cl, 5.63. Found C, 45.89; H, 6.14; N, 15.39; Cl, 5.82.
10. It is proposed that the dimerization occurs via an intermediate oxonium ion generated by attack of acetyl chloride on one equivalent of the aminomethyl furan, subsequent attack by a second equivalent furnishes the desired ammonium salt.



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