New Findings on Degradation of Famotidine Under Basic Conditions: Identification of a Hitherto Unknown Degradation Product and the Condition for Obtaining the Propionamide Intermediate in Pure Form

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ABSTRACT: The degradation behavior of famotidine (**1**) was investigated in 25% ammonia solution and in 2 M NaOH. The hydrolysis of the drug in ammonia resulted in separation of [3-[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionamide (**3**), an impurity listed in British Pharmacopoeia. The treatment with 2 M NaOH resulted in formation of [3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionyl]sulfamide (**2**) and **3**. These products further decomposed to [3-[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propionic acid (**4**) and a heretofore unknown product, **5**. The latter separated out in the reaction mixture as brown shiny crystals. Proton and carbon-13 nuclear magnetic resonance spectroscopy, mass spectrometry, and elemental analysis of the charcoal-treated product established the structure. The formation of **5** is postulated to involve abstraction of a proton from the α-carbon of intermediates **2** and **3** followed by elimination of the thiol moiety. J Pharm Sci 91:253–257, 2002

Keywords: famotidine; degradation; basic conditions; BP impurity; unknown product

INTRODUCTION

The degradation chemistry of famotidine (**1**, [3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]-thio]-N^2-sulfamoylpropionamidine, Figure 1), a highly selective and widely used histamine H_2 receptor antagonist, is described in literature by Junnarkar and Stavchansky.[1] The authors report formation of sulfamoyl amide **2**, amide **3**, and the carboxylic acid **4** as the degradation products of famotidine under both acidic and basic conditions. Generation of two unidentified products under alkaline conditions was mentioned. The pathway proposed for the formation of products **2**–**4** at pH 10 is depicted in Scheme 1a. During studies in our laboratory, crystals were formed when famotidine was reacted both in 25% ammonia and 2 M NaOH solutions. The only product in ammonia was identified as **3**. The condition for obtaining **3** in pure form is not reported in literature, whereas the procedures for isolation of products **2** and **4** are already reported.[2] In 2 M NaOH, the product was characterized as **5**, which is a hitherto unidentified degradation product.

This report provides details of the reactions and presents data on characterization of products **3** and **5**. The results of thin-layer chromatographic (TLC) studies that were carried out to outline the scheme of reaction in 2 M NaOH. The mechanism for the formation of products 3 and 5 is postulated.

RESULTS AND DISCUSSION

Pathway of Degradation of 1 in 2 M NaOH

The decomposition of famotidine was dependent on the reaction conditions. Thus, the treatment of

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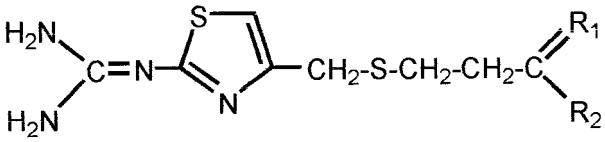
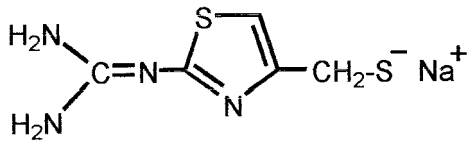


1, $R_1 = NSO_2NH_2$, $R_2 = NH_2$
2, $R_1 = O$, $R_2 = NHSO_2NH_2$
3, $R_1 = O$, $R_2 = NH_2$
4, $R_1 = O$, $R_2 = OH$

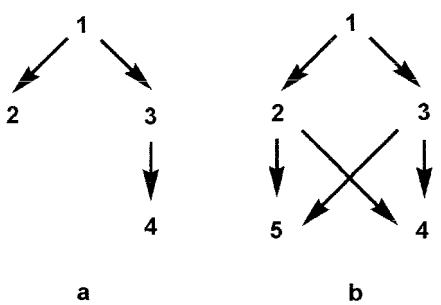


5

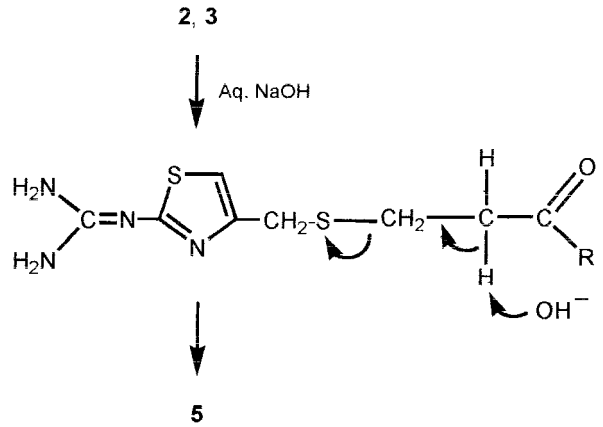
Figure 1. Structures of famotidine (**1**), [3-[[[2-[(diaminomethylene)-amino]-4-thiazolyl]methyl]thio]propionyl]sulfamide (**2**), [3-[[2-[(diaminomethylene) amino]-4-thiazolyl]methyl]thio]propionamide (**3**), [3-[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]-thio]propionic acid (**4**), and the new product (**5**).

1 with 25% ammonia at 60–65°C for 20 min afforded a solid product in 97% yield. The appearance of the band at 1673 cm^{-1} in place of the 1283 cm^{-1} band in the infrared (IR) spectrum of the product is indicative of the hydrolytic cleavage of the $-C(=N-SO_2NH_2)-$ moiety, generating the corresponding amide. The elemental analysis, chemical ionization mass spectrometry (CIMS), IR, ^1H and ^{13}C nuclear magnetic resonance (NMR) data (see *Experimental Section*) are in conformity with the assigned structure **3**.

Treatment of **1** with 2 M NaOH at 80–85°C for 10 min followed by room temperature for overnight resulted in the formation of brown shiny



Scheme 1. (a) Pathway of base-catalyzed hydrolysis of **1** as reported by Junnarkar and Stavchansky,[1] and (b) pathway of degradation of **1** in 2 M NaOH observed in the present study.



Scheme 2. Postulated mechanism for the formation of the new product **5** from **2** and **3**.

crystals, the methanolic solution of which on treatment under reflux with animal charcoal afforded an off-white solid in ~16% yield. The elemental analysis, CIMS, UV, IR, ^1H and ^{13}C NMR data (see *Experimental Section*) are in conformity with the assigned structure **5**.

Anticipating the formation of intermediate products in 2 M NaOH, the progress of reaction was monitored by TLC. The TLC studies revealed that there was initial accumulation of **2** and **3**, but the intensity of spots corresponding to these two intermediates diminished with time with concomitant increase in intensity of spots of **4** and **5**. Authentic samples of **2**, **3**, and **4** were subjected to similar treatment and TLC was employed to monitor the progress of reaction. Compounds **4** and **5** could be identified in reaction mixtures of **2** and **3**. However, **4** remained unaffected, indicating that formation of **5** did not proceed from **4**.

The pathway for the degradation of **1** in 2 M NaOH is summarized in Scheme 1b. In comparison with Scheme 1a proposed by Junnarkar and Stavchansky,[1] Scheme 1b provides more detailed information regarding the degradation pathway.

Postulated Mechanism of Degradation of 1 to 5 Under Aqueous NaOH and 1 to 3 in Aqueous Ammonia

The formation of **5** may be explained as a result of base-catalyzed elimination from **2** and **3**, via the proton abstraction from the α-carbon of the carbonyl group (Scheme 2). The anion of **5** as a sodium salt gets separated from the reaction mixture. The driving force for the elimination of the thiol moiety is the formation of α,β-unsaturated

carbonyl compound and the good leaving group property of the thiolate anion. The apparent stability of **4** under this condition (not being converted to **5**) reflects the inability of the similar elimination to be operative with **4** (as sodium salt), because the proton abstraction from the α-carbon of the carboxylic group will involve the generation of dianionic intermediate. In general, metal hydroxides are not strong bases to generate the dianion from the carboxylate anion.

The decomposition of **1** under aqueous acidic and alkaline conditions will be dependent on competitive hydrolytic cleavage of the amide function (to give rise to **2**) or the sulfamide function (to afford **3**) or of both (to yield **4**) and the elimination via abstraction of one of the $-H_2C-C(=N-)-$ protons (resulting in the formation of 5). The ease of nucleophilic attack on C=N or C=O via the tetrahedral mechanism should make the hydrolytic cleavage more facile compared with the competitive elimination process that will be dependent on the acidity of the methylene protons as well as the basicity of the medium. Therefore, under acidic conditions, because **1** exists mostly in the protonated form,[1] the nucleophilic attack leading to the formation of **2**, **3**, and **4** becomes the predominant pathway. On the other hand, because **1** exists mostly in the undissociated form under alkaline conditions,[1] one might expect the elimination pathway to be operative along with the hydrolytic cleavage. However, the intermediate formation (TLC) of **2** and **3** clearly indicate that during the conversion of **1** to **5**, under aqueous alkali treatment conditions, the hydrolytic cleavage precedes the elimination process. This sequence is further supported by the conversion of **2** and **3** to 5 through individual treatments. The direct conversion of **1** to 5 may be ruled out primarily on the basis of (i) much less acidic character of the $-H_2C-C(=N-)-$ protons compared with that of $H_2C-C(=O)-$ protons and (ii) susceptibility to hydrolytic cleavage of the imine group. Even the elimination pathway to convert **4** to **5** under the aqueous alkali treatment conditions is unlikely because it will involve the formation of the dianionic species that can only be generated by the action of very strong base, such as lithium diisopropylamide.[3]

The behavior of **1** in ammonia, leading to **3** as a sole product, may be explained on the basis of exchange of ammonia (a stronger nucleophile compared with hydroxyl anion) with sulfamide followed by hydrolysis of the imine moiety. The basicity of ammonia (pK_b 4.75) may not be sufficient enough to abstract the α-hydrogen for the elimination and the formation of **5** to take place. Under these conditions, the hydrolysis to acid **4** is also unlikely.

CONCLUSIONS

The establishment of degradation chemistry and intrinsic stability of a new drug under variety of conditions (temperature, humidity, pH, oxidation, and light) is listed as a requirement under the current ICH[4] and USFDA[5] guidelines on stability testing. For old and established drugs, the European Pharmacopoeia as well as the British Pharmacopoeia list impurities, including degradation products that are supposed to be controlled in the active substance. The identification of degradation products and establishment of conditions for their isolation in pure form, therefore, has assumed importance.

In this context, the present study on famotidine adds information to the existing knowledge on the degradation of this drug. The study provides evidence about the formation of a hitherto unknown degradation product **5** from **1** under strong alkaline conditions. The pathway of the degradation of **1** under strong alkali conditions is described, and the mechanism for conversion of **1** to **5** is postulated. The study also suggests condition for preparation of **3** in pure form. This degradation product is listed as an impurity in British Pharmacopoeia[6] and is required to be controlled in the pure sample of **1**. The knowledge of conditions under which it can be prepared in pure form is expected to be useful for its availability as a standard.

EXPERIMENTAL SECTION

Materials

Famotidine was generously provided by Torrent Pharmaceutical Ltd. (Indrad, Gujrat, India). Compounds **2** and **4** were synthesized by the reported method.[2] All other chemicals were of analytical grade.

Spectral Analyses

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer in DMSO-d_6. ^{13}C NMR of **3** was taken in MeOH-d_4. Signals

of exchangeable protons were confirmed by addition of 0.5 mL of D_2O. Chemical shifts are reported in ppm (δ) value relative to tetramethylsilane as internal standard for ^1H NMR and in ppm relative to the solvent for ^{13}C NMR. Fourier transform IR (FTIR) spectra were determined in a KBr disc with NICOLET IMPACT 410 spectrometer. Ultraviolet (UV) spectra were recorded on a Beckmann DU 7400 spectrophotometer. Elemental analyses were performed on Elementar Vario EL instrument. CIMS analysis was done on Shimadzu GC-MS QP 5000 through direct injection to the mass probe using methane (15 lb/In^2) as reagent gas and helium (1 mL/min) as carrier gas (temperature program: 25– 40°C/min–320°C; run time: 15 min; detector volts: 1.5 kV).

Thin Layer Chromatography (TLC)

TLC was performed in an ascending mode. TLC sheets (20 × 20 cm), precoated with silica gel $60F_{254}$ (Merck, Germany), were used. The solvent system was ethyl acetate:methanol:toluene:ammonia (4.0:2.5:2.0:0.2).[1] A 150-mL quantity of the solvent was charged to the TLC developing tank lined with a filter paper. Equilibration was carried out for 45 min. The separation of products was detected in a UV light chamber. The R_f values for **1**–**5** were 0.59, 0.33, 0.64, 0.22, and 0.75, respectively.

Reaction of 1 in 25% Ammonia

First, 2.5 g of 1 was dissolved in aqueous NH_3 (50 mL, 25%) and then the solution was heated at 60–65°C for 20 min in a round-bottomed flask fitted with a reflux condenser. The reaction mixture was cooled to room temperature (28–32°C) and was left overnight (~12 h) in a stoppered flask. The solid that separated out was collected, washed with water (2 × 10 mL) and dried under vacuum at room temperature for 3 h to afford **3** (1.87 g, 97 %): FTIR: ν(cm^{-1}) 1650, 1673, 3406, and 3431; ^1H NMR (DMSO-d_6): δ 2.33 (t, 2H, $-S-C\mathbf{H_2}-CH_2-$), 2.65 (t, 2H, $-S-CH_2-C\mathbf{H_2}$), 3.58 (s, 2H, $-C\mathbf{H_2}-S-CH_2-$), 6.47 (s, 1H, $-C=C\mathbf{H}-S-$), 6.83 [brs, 5H, $-N=C(N\mathbf{H_2})_2$ and 1H of amide protons, exchangeable with D_2O], and 7.33 (brs,1H of amide protons, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6): δ 26.97 ($-S-\mathbf{C}H_2-CH_2-$), 31.43 ($-S-\mathbf{C}H_2-C=$), 35.24 ($-S-CH_2-\mathbf{C}H_2-$), 104.5 ($-S-\mathbf{C}H=C-$), 147.94 ($-\mathbf{C}=CH-S-$), 156.94 ($-N-\mathbf{C}=N-$), 173.09 ($-\mathbf{C}=O$), 175.45 ($-N=\mathbf{C}(NH_2)_2$); CIMS m/z 188 ($M+1$): C, H, N, S (calculated %: C = 37.0, H = 5.02, N = 27.02, S = 24.71; observed %: C = 36.68, H = 4.93, N = 27.44, S = 25.07).

Reaction of 1 in 2 M NaOH

First, 5.0 g of **1** was dissolved in 250 mL of 2 M NaOH and then the mixture was heated to 80–85°C for 10 min. The mixture was cooled to room temperature and left overnight. The brown shiny crystals that separated out were collected and washed with water (2 × 10 mL). The crystals were dissolved in methanol (10 mL), treated with animal charcoal (~100 mg) under reflux for 15 min, and filtered. The filtrate was concentrated, and the residue was dried under vacuum at room temperature for 3 h to afford **5** (500 mg, 16%) as an off-white solid: mp, 194–199°C; UV (MeOH) λ_{max} 289 nm (log ε: 4.66); FTIR ν(cm^{-1}): 1484, 1544, 1600, 3382, and 3431; ^1H NMR (DMSO-d_6): δ 3.64 (s, 2H, $-C\mathbf{H_2}-SNa$), 6.48 (s, 1H, $-C=C\mathbf{H}-S$), 6.88 (brs, 4H, $-N=C(N\mathbf{H_2})_2$, exchangeable with D_2O); ^{13}C NMR (MeOH-d_4): δ 40.053 ($-\mathbf{C}H_2-SNa$), 107.97 ($-C=\mathbf{C}H-S-$), 148.077 ($-\mathbf{C}=CH-S$), 158.92 ($=N-\mathbf{C}=N-$), 175.66 ($-N=\mathbf{C}(NH_2)_2$); CIMS m/z 189 (MH^+): C, H, N, S (calculated %: C = 28.57, H = 3.33, N = 26.66, S = 30.47; observed %: C = 28.78, H = 3.34, N = 26.38, S = 30.08).

Because of the low yield of the product **5**, it was considered prudent to repeat the reaction and follow it by TLC to look for the formation of intermediary products (see *Results and Discussion*).

Reaction of 2 in 2 M NaOH

First, 0.5 g of **2** was dissolved in 25 mL of 2 M NaOH. Then, the solution was heated at 40–45°C for 2 h and at 60–65°C for 3 h. The reaction was followed by TLC to identify the intermediate products. The mixture was cooled to room temperature and left overnight. The brown shiny crystals that separated out were collected, washed with water, and treated with animal charcoal as already described to afford 30 mg of **5**.

Reaction of 3 in 2 M NaOH

First, 0.5 g of **3** was added to 2 M NaOH (25 mL) and then the mixture was heated to 80–85 °C for 1 h. The reaction was followed by TLC. The solution was cooled to room temperature and left overnight. The brown shiny crystals that separated out were collected, washed with water, and

treated with animal charcoal as already described to afford 33 mg of **5**.

Reaction of 4 in 2 M NaOH

First, 0.5 g of **4** was dissolved in 2 M NaOH (25 mL) and heated to 80–85°C for 1 h. Then, the reaction mixture was cooled to room temperature and left overnight. No solid precipitated out in this reaction mixture. TLC also revealed no change.

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