Synthesis of potential related compounds of Cefdinir

Korrapati. V. V. Prasada Rao,[a] Ramesh Dandala,[a*] Ananta Rani,[a] and Andra Naidu[b]

[a] *Chemical Research Department, APL Research Center, Hyderabad-500 072, India*
[b] *J. N. T. University, Kukatpally, Hyderabad-500 072, Andhra Pradesh, India*
E-mail: rdandala@aurobindo.com

Abstract

The synthesis of three contaminants of Cefdinir (**1**), formed during the preparation of Cefdinir bulk drug, is described. The products identified as (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid-5-oxide (**2**), (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-3-ene-2-carboxylicacid (**3**) and (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-methyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (**4**).

Keywords: 7-AVNA, Cefdinir, pharmaceuticals, synthesis, contaminants

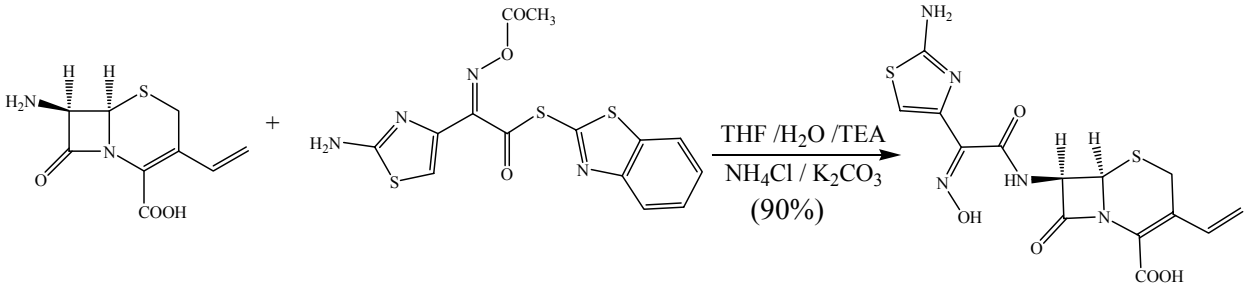
Introduction

Cefdinir **1** is [*syn*-7- [2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid]. It is a third generation cephalosporin antibacterial drug for oral administration.[1] The most remarkable future of Cefdinir is the excellent activity against staphylococcus species.[2] Several methods are reported in the literature for the preparation of Cefdinir [3-7], but the related compounds were not discussed. However, the degradation kinetics of cefdinir has been cited in the literature.[8] The preparation of these three contaminants has been necessary for the preparation of reference compounds for the quality control of bulk drugs and drug formulations, and pathways have been developed starting from the parent Cefdinir **1**.

Results and Discussion

Cefdinir was prepared, starting from 7-amino-3-vinyl-3-cephem-4-carboxylic acid **5** by acylating with compound **6** followed by hydrolysis with base (Scheme 1). During the analysis of different batches of Cefdinir, three unknown impurities **2, 3** and **4** were detected whose area percentage

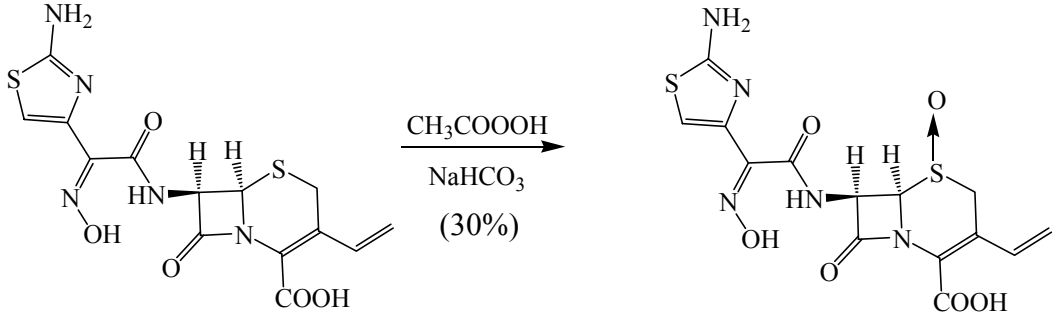
ranged from 0.05 % and 0.15%. A comprehensive study has been carried out to synthesize these impurities.



5 **6** **1**

Scheme 1

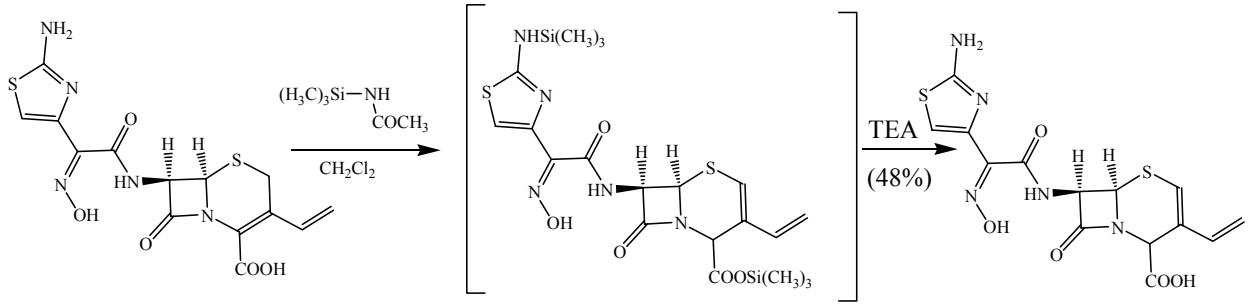
Sulfoxides are very common impurities in cephalosporin antibacterial compounds. The elimination of these compounds was very difficult from the finished products. Cefdinir sulfoxide **2** was observed up to 0.1% in most of the Cefdinir batches prepared in the laboratory. Therefore it was necessary to synthesize the sulfoxide in pure form for the validation of this impurity in the Cefdinir bulk drug. Cefdinir sulfoxide was prepared by the oxidation of Cefdinir in 30% yield by using per acetic acid as an oxidizing agent (Scheme 2).



1 **2**

Scheme 2

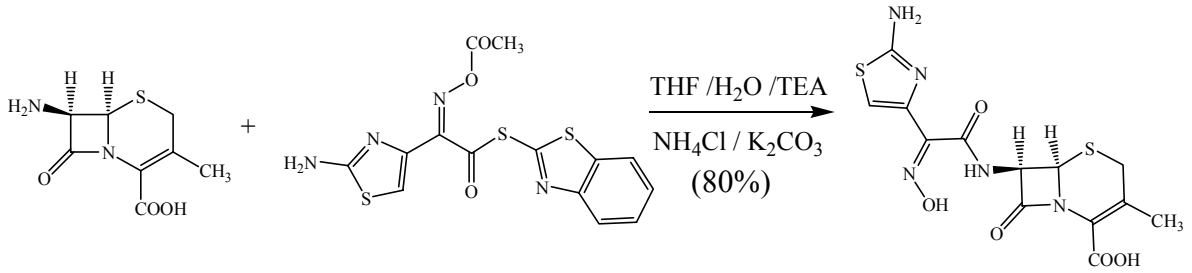
Treating the silylated Cefdinir **1** with triethylamine in methylene chloride provided a more selective approach for the preparation of delta-2 Cefdinir **3**. During the monitoring by HPLC, 60% of delta-2 Cefdinir was formed, which was further purified by acid-base treatment to obtain compound **3** in 48 % yield. (Scheme 3).



1 **3**

Scheme 3

Compound **4** was formed due to presence of desacetoxycephalosporanic acid **7** as an impurity in the key raw material 7-aminio-3-vinyl-3-cephem-4-carboxylic acid **5**. Compound **4** was prepared in 80% yield by the acylation of compound **7** with compound **6** followed by basic hydrolysis. (Scheme 4).



7 **6** **4**

Scheme 4

Conclusions

A procedure has been described for the preparation of three new impurities formed during the preparation of Cefdinir bulk drug in quite good yield and purity.

Experimental Section

General Procedures. All melting points were determined with a Palmon melting point apparatus. ^{1}H-NMR and ^{13}C NMR analysis were recorded on a Bruker 300 MHz and 75 MHz spectrometer respectively. Chemical shifts are reported in *ppm* downfield from TMS as internal standard. Mass spectra were measured on Perkin Elmer PE SCIEX-API 2000 mass spectrometer.

Analytical HPLC[9] were run with Hypersil BDS C18 column with the dimension of 150X4.6 mm i.d (Thermo-Electron) at 254nm.

***syn*-7-[2-(2-Aminothiazole-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (1).** (Z)-2-(2-Aminothiazol-4-yl)-2-acetoxyiminothioacetate, **6** (138.38 g, 0.366 mol) was added to a suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid, **5** (75.0 g, 0.331mol) in tetrahydrofuran (750 ml) under nitrogen atmosphere. DM Water (375 ml) was added to the resulting suspension at 15-20°C in 10-15 min. Thereafter triethylamine (36.75 g, 0.363 mol) was added in 30 min at 18-20°C and stirred the reaction mass for 5 h at the same temperature. Methylene chloride (750 ml) was added followed by DM water (375 ml) and stirred the reaction mass for 10 min. The aqueous layer was separated and washed with methylene chloride (375 ml). The aqueous layer was degassed under reduced pressure to remove the traces of solvents. pH of the aqueous layer was adjusted to 8.0 and ammonium chloride (0.953 mol) was added. Thereafter 20% potassium carbonate was added by maintain the pH 8.0-8.20 at 20-25°C in 30 min. After potassium carbonate addition stirred the reaction mass for another 10 min.pH was adjusted to 5 with 10%v/v, aqueous sulfuric acid (100 ml) at 20-25°C. Thereafter temperature was raised to 35-40° and pH adjusted to 2.5-2.6 with 10% aqueous sulfuric acid (100 ml). The solid was filtered and washed with water (750 ml) and dried, to yield **1** (118.0 g, 90%) as a pale yellow solid; purity 99% (by HPLC); mp 180-190°C (decompose) (lit, [7] 180-187°C); IR (KBr, cm^{-1}): 3302, 3176, 1784, 1668, 1611, 1429, 1545, 1350, 1334, 1050, 1017; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.55&3.83 (ABq, 2H), 5.19 (d, 1H), 5.30 (d, 1H), 5.60 (d, 1H), 5.79 (dd, 1H), 6.67 (s, 1H), 6.80-6.90 (m, 1H), 7.10 (bs, 2H), 9.50 (d, 1H), 11.33 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) 24.1, 58.6, 59.5, 108.4, 118.6, 125.7, 126.0, 132.6, 143.9, 149.0, 164.0, 164.6, 164.8, 169.2; MS (ESI, *m/z*): 396.2 $[M+H]^+$. Anal. Calcd. For $C_{14}H_{13}N_5O_5S_2$: C, 42.49; H, 3.29; N, 17.70; S, 16.19. Found: C, 42.33; H, 3.28, N, 17.63, S, 16.17 %.

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid –5-oxide (2). Sodium bicarbonate (3.6 g, 0.0379 mol) was added to a suspension of syn-7- [2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid, **1** (10 g, 0.0253 mol) in 30 min at 10-15°C and stirred for 30 min to get a clear solution. The resulting solution was cooled to 2-5°C and 30% w/w, per acetic acid (7.03 g, 0.0277 mol) was added in 30 min at 2-5°C. Thereafter stirred the reaction mixture for 2 h at the same temperature. pH was adjusted to 2.8 with 10% w/w sulfuric acid and stirred for 1h. The reaction mass was diluted with water (200 ml). The solid was filtered and washed with water and dried to yield **2** (3.1 g, 30%) as an off-white solid. mp 177-182°C (decompose); IR (KBr, cm^{-1}): 3320, 3150, 2900, 1777, 1666, 1633, 1425, 1525, 1303, 1115, 1023; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.55&4.29 (2d, 2H), 5.04 (d, 1H), 5.34 & 5.60 (2d, 2H), 5.98 (dd, 1H), 6.81 (s, 1H), 7.08 (dd, 1H), 7.30 (brs, 2H), 8.59 (d, 1H), 11.67 (brs, 1H); ^{13}C- NMR (75 MHz, DMSO-d_6) 43.4, 58.8, 67.0, 108.0, 118.6, 120.3, 125.4, 133.2, 143.1, 148.4, 163.3, 163.9, 164.5, 169.2; MS (ESI, *m/z*): 412.2 $[M+H]^+$. Anal. Calcd. For $C_{14}H_{13}N_5O_6S_2$: C, 40.87; H, 3.18; N, 17.02; S, 15.59. Found: C, 40.90; H, 3.20, N, 17.03, S, 15.60 %.

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-3-ene-2-carboxylic acid (3). N-trimethylsilylacetamide (19.90 g, 0.152 mol) was added to a suspension of syn-7- [2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-car-boxylic acid, **1** (20 g, 0.0506 mol) in methylene chloride (200 ml) and stirred for 30 min to get a clear solution. The resulting solution was cooled to 2-5°C and triethylamine (5.63 g, 0.0557 mol) was added in 30 min at 2-5°C. Thereafter stirred the reaction mixture for 24 h at 25-30°C temperature. Water (200 ml) was added and stirred for 10 min. The aqueous layer was separated and washed with methylene chloride (50 ml). The aqueous layer was cooled to 2-5°C and pH adjusted to 3.0 with 10 % w/w sulfuric acid (10 ml). The resulting slurry was stirred for 2 h. The solid was filtered and washed with water and dried to yield 12.5 g (62.5%) of **2** as a yellow amorphous powder. This solid was suspended in water (200 ml) and pH adjusted to 7.5-8.0 with aqueous sodium bicarbonate at 20-25°C to get a clear solution. Carbon (1 g) was added and stirred for 30 min. Carbon was filtered washed with water (25 ml). The filtrate was cooled to 5-10°C and pH adjusted to 3.0 with 10% w/w sulfuric acid. The solid was filtered, washed with water (50 ml) and dried to yield **3** (6 g, 48%) as an off-white solid. mp 255-260°C (decompose); IR (KBr, cm^{-1}): 3300, 3196, 3000, 1760, 1674, 1614, 1401, 1533, 1370, 1310,1113, 1046; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 4.73 (s, 1H), 4.89 & 5.35 (2d, 2H), 5.36 (d, 1H), 5.45 (dd, 1H), 6.27 (dd, 1H), 6.44 (s, 1H), 6.70 (s, 1H), 7.38 (s, 2H), 9.42 (d, 1H), 11.61 (brs, 1H); ^{13}C- NMR (75 MHz, DMSO-d_6) 53.02, 54.30, 60.20, 107.80, 111.40, 121.10, 126.60, 137.0, 144.60, 149.50, 163.40, 164.60, 169.0, 169.90; MS (ESI, *m/z*): 396.2 $[M+H]^+$. Anal. Calcd. For $C_{14}H_{13}N_5O_5S_2$: C, 42.49; H, 3.29; N, 17.70; S, 16.19. Found: C, 42.60; H, 3.32, N, 17.70, S, 16.25 %.

***syn*-7-[2-(2-Aminothiazole-4-yl)-2-hydroxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid (4).** (Z)-2-(2-aminothiazol-4-yl)-2-acetoxyiminothioacetate, **6** (19.60 g, 0.0518 mol) was added to a suspension of desacetoxycephalosporanic acid, **7** (10 g, 0.0467 mol) in tetrahydrofuran (750 ml) under nitrogen atmosphere. DM water (50 ml) was added followed by triethylamine (5.19 g, 0.0514 mol) was added in 30 min at 18-20°C and stirred the reaction mass for 5 h at the same temperature. Methylene chloride (100 ml) was added followed by DM water (50 ml) and stirred the reaction mass for 10 min. The aqueous layer was separated and washed with methylene chloride (50ml). The aqueous layer was degassed under reduced pressure to remove the traces of solvents. pH of the aqueous layer was adjusted to 8.0 and ammonium chloride (7.17 g, 0.134 mol) was added. Thereafter 20% w/v, potassium carbonate (37 ml) was added by maintain the pH 8.0-8.20 at 20-25°C in 30 min. After potassium carbonate addition stirred the reaction mass for another 10 min. pH was adjusted to 5 with 10% v/v, aqueous sulfuric acid (13 ml) at 20-25°C. Thereafter temperature was raised to 35-40° and pH adjusted to 2.5-2.6 with 10% v/v, aqueous sulfuric acid (12 ml). The solid was filtered and washed with water (100 ml) and dried, to yield **4** (13.75 g, 80%) as an off white solid; purity 98% (by HPLC); mp 177-182°C (decompose); IR (KBr, cm^{-1}): 3297, 3200, 2980, 1760, 1658, 1622, 1400, 1534, 1380, 1365, 1015; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.02 (s, 3H), 3.35&3.55 (ABq, 2H), 5.10 (d, 1H), 5.71(dd, 1H), 6.69 (s, 1H), 7.40 (brs, 2H), 9.49 (d, 1H), 11.46 (brs, 1H); ^{13}C-NMR (75

MHz, DMSO-d_6) 20.3, 30.0, 58.2, 59.3, 108.1, 123.7, 131.2, 142.7, 148.6, 164.4, 169.4; MS (ESI, *m/z*): 413 $[M+H]^+$. Anal. Calcd. For $C_{13}H_{13}N_5O_5S_2$: C, 40.72; H, 3.42; N, 18.27; S, 16.73; Found: C, 40.73; H, 3.44, N, 18.30, S, 16.80 %.

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References and Footnotes

1. Ternansky, R. J.; Christofer, F.; Bell, W.; Theresea, G.; Skaggs, S.; Kasher, *J. Antibiot.* **1993**, *46*, 1897.
2. Inamoto, Y.; Chiba, T.; Kamimura, T.; Takaya, T. J. *Antibiot.* **1988**, *41*, 828.
3. Takaya, T.; Hisashi, T. US. Pat 4,559,334: *Chem. Abstr*. **1984**, *101*, 130505.
4. Lee, G. S.; Chang, Y. K.; Chun, J. P.; Kho, J. H. US. Pat 6,093,814: *Chem. Abstr*. **1997**, *127*, 149040
5. Rajkumar, WO 121154: *Chem. Abstr*. **2002**, *144*, 51373.
6. Sakane, J.; Kazuo, Y. ES Pat 2,013,828: *Chem. Abstr*. **1993**, *113*, 23533
7. Takaya, T.; Shirai, F.; Nakamura, H.; Inaba, Y. US. Pat 4,935,507: *Chem. Abstr.* **1989,** *111*, 96960x.
8. Okamoto, Y.; Kiriyama, K.; Namiki, Y.; Matsushita, J.; Fujioka, M.; Yasuda, T. J. Pharmaceutical. Sciences. **1996**, *85*, 976.
9. HPLC analysis was carried out for compounds 1, 2, 3, 4, 5, 6 and 7.