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# SYNTHESIS OF POTENTIAL IMPURITY OF CEFUROXIME ACID

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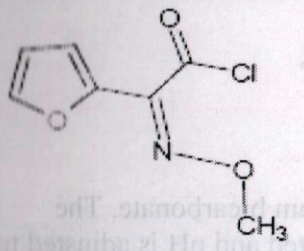
## ABSTARCT

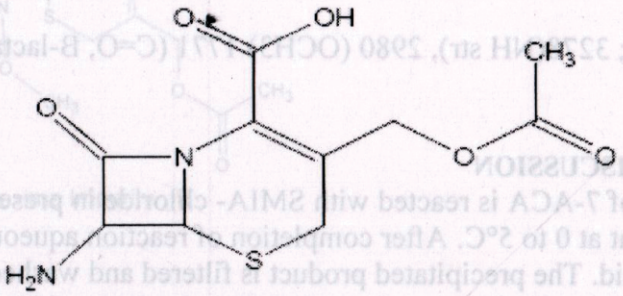
Synthesis of Cefuroxime Acid impurity (I) has been described by N-acylation of 7-Amino cephalosporanic Acid (II) and excess of SMIA Chloride (III).

## 1. INTRODUCTION

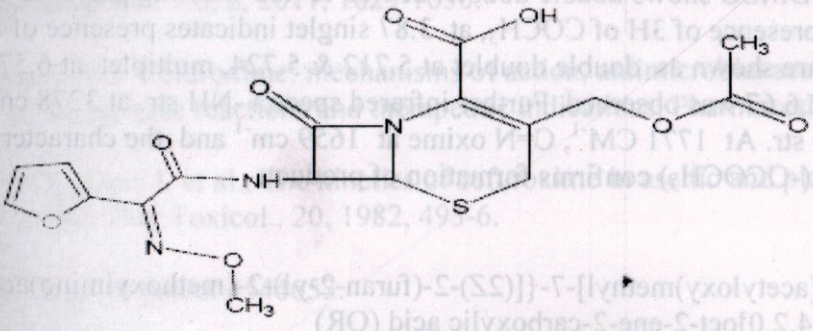
The Cefuroxime axetil, (R,S)-1-acetoxyethyl (Z)-3-carbomoyloxymethyl-7-[2-(2-furyl)-2-(methoxyimino)-acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, is the 1-acetoxyethyl ester of cefuroxime. Cefuroxime is a cephalosporin antibiotic having a broad spectrum of activity against both gram-positive and gram-negative microorganisms. It is prescribed for mild to moderately severe bacterial infections of the throat, lungs, ears, skin, sinuses, urinary tract, and gonorrhoea. Cefuroxime axetil is also prescribed in the early stages of Lyme disease. One of the raw material for cefuroxime axetil is cefuroxime Acid. During the course of the synthesis of Acid , Cefuroxime Acid impurity is generated due to left over unreacted 7-ACA , which reacts competitively with SMIA Chloride forming an amide. In general, for the preparation of amides , one can adopt the reactions like Beckmann rearrangement, Schimidt reaction, nitrile hydrolysis, Ugi reaction, Bodroux reaction, etc. In present work we had adopted schotten-Baumann reaction , where an acid chloride, SMIA Chloride, (2Z)-Furan-2-yl (Methoxyimino)-ethanoyl chloride is reacted with an amine, 7-Amino Cephalosporanic acid (7-ACA) and is confirmed by spectral analysis.




SMIA Chloride (III)




7-ACA (II)




Cefuroxime Impurity-B (I)

Cefuroxime Impurity (I) is described in the monograph of Cefuroxime in European pharmacopeia as impurity-B and this is a common process related impurity in Cefuroxime.

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## 2.EXPERIMENT

**a)SMIA chloride preparation:** To a mixture of 500 ml dichloro methane is mixed with 45 gms of Phosphorous penta chloride and cooled to -30°C. Added 50 ml of Dimethyl acetamide in 15 minutes. Charged 39 gms SMIA ammonium salt. Raised temp to -10°C. Agitated for 90 minutes. Charged 180 ml of water keeping temp below 0°C. Stired for 10 minutes and settled for 15 minutes and separated organic layer. Washed organic layer with 180 ml & 90 ml water at less than 0°C. Then separated organic layer & preserved.

**b)7-ACA dissolution:** Dissolved 50 gms 7-ACA suspended in400 ml water with 10% sodium bicarbonate solution at < 5°C & pH 7.5.

**c)Impurity-B synthesis & isolation:** To the 7-ACA solution (b) added SMIA chloride solution (a) slowly in 30 minutes by maintaining the pH at 6.5 to 7.0 by 10% sodium bicarbonate solution at <5°C. Stirred for 2 hours. Separated the organic layer and aqueous layer. To aqueous layer, add 5% HCl solution slowly in 120 minutes at <5°C to adjust pH 3.0 ± 0.2, to obtain precipitate of Cefuroxime acid Impurity-B. Agitated for 1hr at 0 to 5°C. Filtered and washed with 200 ml water twice. Again washed with 100 ml methanol twice. Dried the wet cake under vacuum at <40°C to obtain 50 gms Cefuroxime acid impurity-B.

Spectral data: IR (KBr, $V_{max}$ $Cm^{-1}$): NH-stretching 3276 cm-1, β-lactam stretching 1771 cm-1, C=N oxime & C=O amide stretching at 1659 cm-1,
Purity : 98.72% by HPLC
1H NMR (400 MHz, DMSO): 1.976 (S, 3H, CO-CH3); 3.414 &3.46, 3.572&3.618 (dd, 2H, S-CH2); 3.844 (S, 3H, NOCH3); 4.63 &4.662 (dd,2H, CH2 OCO); 4.894& 4.926, 5.091 &5.103 (dd, 2H, S-CH-CH); 5.712 & 5.724, 6.575,6.58,6.584,6.588 & 6.662,6.67 (dd,m, dd, 3HFurane ); 7.723 (S, 1H NH), 9.76 & 9.781 (d, 1H, COOH),
IR (KBr, $V_{max}$ $cm^{-1}$ ); 3278(NH str), 2980 (OCH3) 1771 (C=O, B-lactam, 1659 (C=N) ,
MS (m/e): 423

## 3.RESULTS AND DISCUSSION

The sodium salt of 7-ACA is reacted with SMIA- chloride in presence of base sodium bicarbonate. The reaction is carried out at 0 to 5°C. After completion of reaction aqueous layer is separated and pH is adjusted to 3 by hydrochloric acid. The precipitated product is filtered and washed with water & Methanol. Dried the wet material at 40°C to obtain Cefuroxime impurity –B. It is observed in the study that higher temperature & use of strong alkali like alkali hydroxide will hydrolyse the acetyl group. Hence the study is conducted at around pH 7.5 and the conversion is 97% on HPLC.

1H NMR spectra of compound in DMSO shows double doublet at 4.65 &4.68 showing presence of 2H of $CH_2$ OCO & at 2 .01 singlet showing presence of 3H of $COCH_3$, at 3.87 singlet indicates presence of 3H of , $NOCH_3$ and presence of 3 H of furan are shown as double doublet at 5.712 & 5.724, multiplet at 6.575, 6.58, 6.584,6.588 & double doublet at 6.662,6.67 was observed. Further infrared spectra -NH str. at 3278 $cm^{-1}$,-$OCH_3$ bending at 2980 $cm^{-1}$ : B-lactam C=O str. At 1771 $CM^{-1}$, C=N oxime at 1659 $cm^{-1}$ and the characteristic mass at m/z 423 and its 1st fragment at 364 (-$OCOCH_3$) confirms formation of product.

Abbreviations:

(I) Cefuroxime IMP- B 3-[(acetyloxy)methyl]-7-{[(2*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (OR) (6R,7S)-3(acetyloxymethyl)-7-[[(2Z)-2-(2-furyl)-2-methoxyimino-acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct2-ene-2-carboxylic acid

(II) ACA, 7-Amino Cephalosporanic acid : 3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(III) SMIA Chloride ; (2*Z*)-furan-2-yl(methoxyimino)ethanoyl chloride

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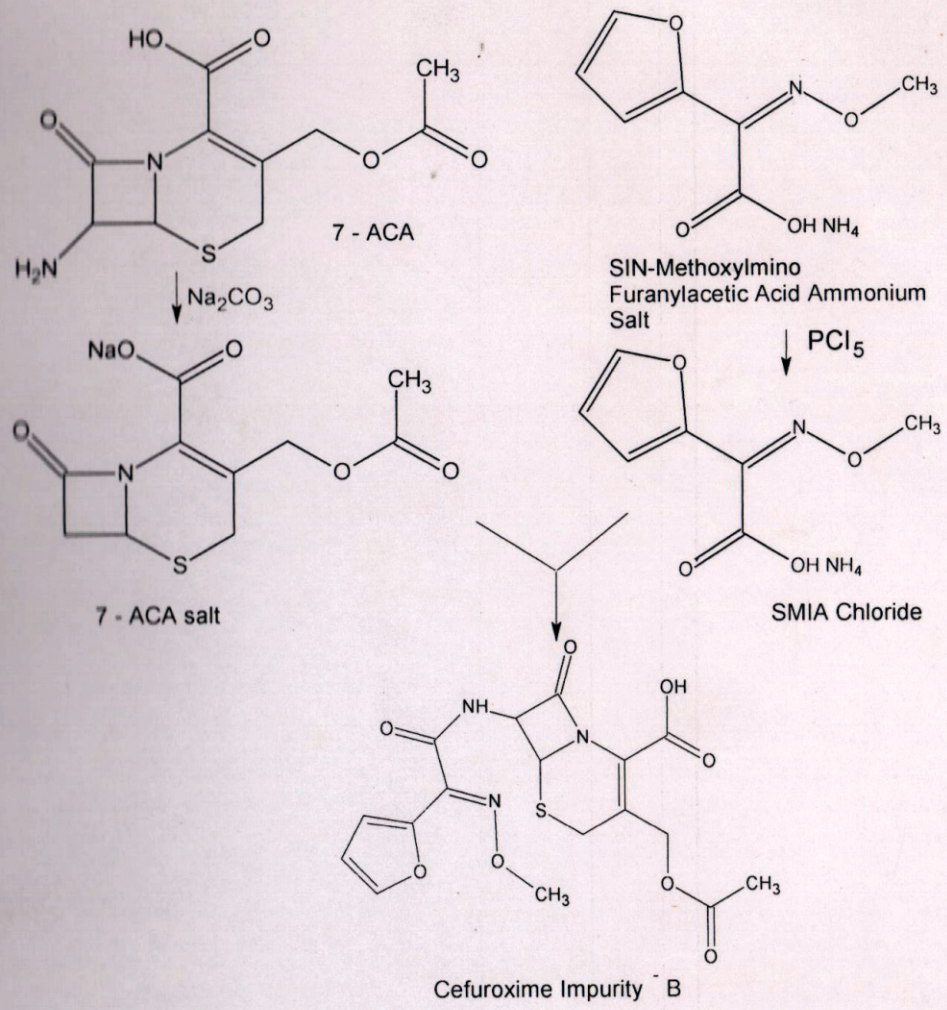


## REFERENCES

Analytical profiles of Drug substances & Excipients, 20, 1991, 209-236

European pharmacopoeia, 7.0, 2, 2011, 1629-1630.

Gold B, Rodriquez WJ. Cefuroxime: mechanisms of action, antimicrobial activity, pharmacokinetics, clinical application, adverse reactions and therapeutic indications, Pharmacotherapy, 3, 1983, 82-100.

Lechi A, Arosio E, Xerri L et al., The kinetics of cefuroxime in ascitic and pleural fluid, Int.J.Clin.Pharmacol.Ther.Toxicol., 20, 1982, 493-6.

US patent 3974173, US patent 4544653.

Windholz M, ed., The Merck index, 10th ed., Rahway, NJ, Merck & Co., Inc., 1983, 272.