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Process for the Synthesis of Carbamate of Cefpodoxime Proxetil

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Carbamate of cefpodoxime proxetil is prepared by reaction of cefpodoxime proxetil with isopropyl chloroformate in presence of N-methyl morpholine.

Key Words: Synthesis, Carbamate of cefpodoxime proxetil.

INTRODUCTION

The title compound is a potential impurity that can form during the manufacturing process of cefpodoxime proxetil*, an antibiotic which is useful for treatment of otitis media, pharyngitis and sinusitis and also for the use as oral continuation therapy when intravenous cephalosporins are no longer needed for continuous therapy. To the best of our knowledge, there is no literature information available on carbamate** of proxetil or on its process for synthesis. Therefore, the synthesis of the title compound is explored and thereby a pharmacist can utilize the process for its synthesis and confirm the presence of this compound as an impurity in the active pharmaceutical ingredient (cefpodoxime proxetil). The probable formation of the carbamate impurity in cefpodoxime proxetil is outlined herein (Fig. 1).

Presence of isopropyl chloroformate in the compound (**V**) may be a source and lead to the formation of carbamate impurity in cefpodoxime proxetil. In general triethyl amine[1-3], DMAP[4], pyridine[5-9], morpholine[10] and inorganic bases[1,9] are used for the preparation of carbamate.

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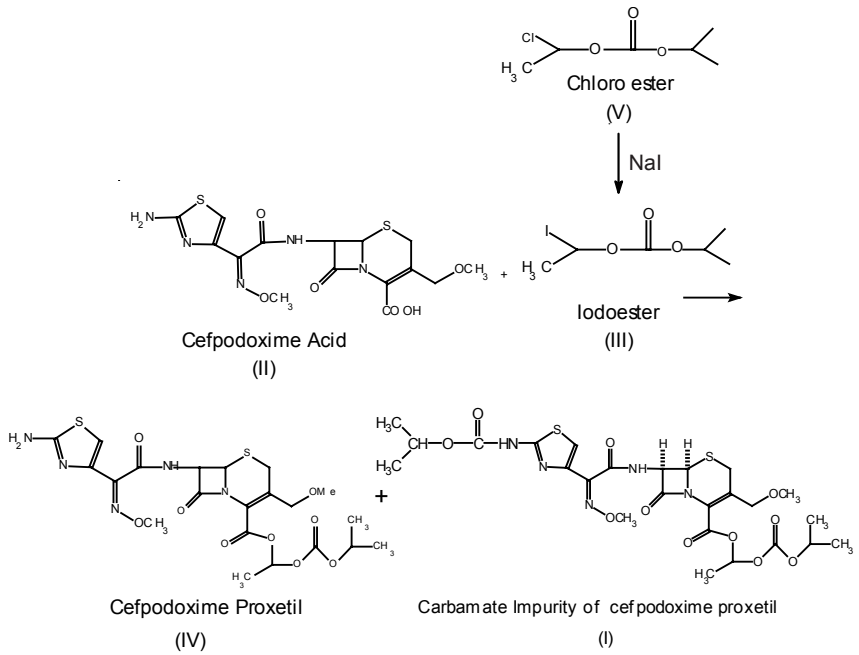
*(6R,7R)-7-[[(2Z)-(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxymethyl-8-oxo-5-thia-1-azabicyclo[[4.2.0]oct-2-ene-2-carboxylic acid 1-[[(1-ethylethoxy)carbonyl]oxy]ethyl ester.

**(6R,7R)-7-[[(2Z)-(2-Isopropoxycarbonylamino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxymethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylicacid 1-[[(1-methylethoxy) carbonyl]oxy]ethyl ester.



(Fig. 1)

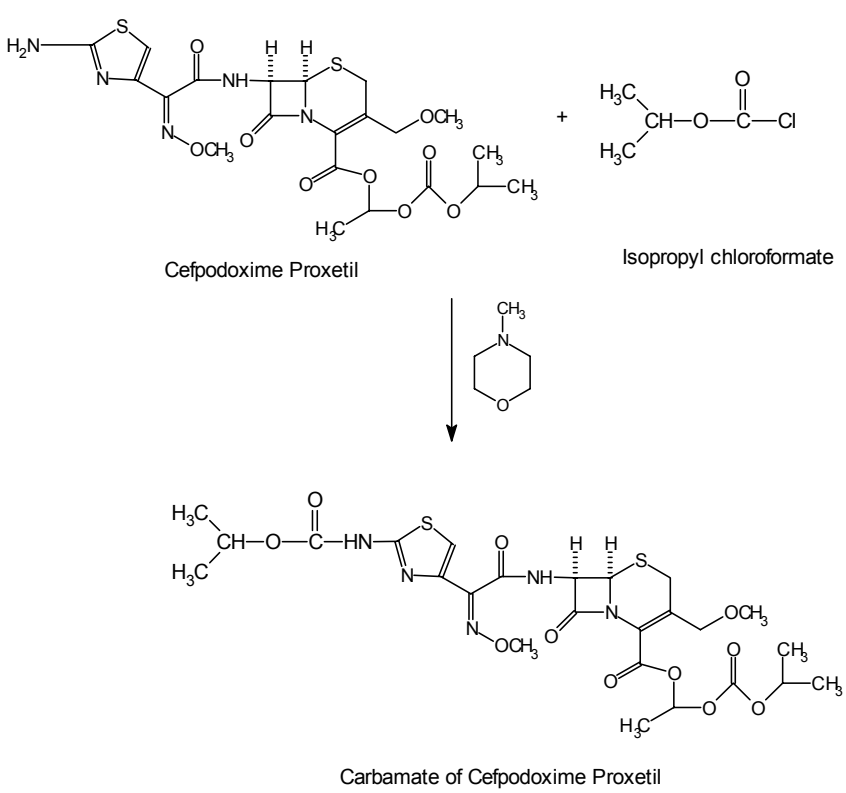
EXPERIMENTAL

Preparation of carbamate of cefpodoxime proxetil: Isopropyl chloroformate (76.76 g, 0.626 mol) was added to a solution of cefpodoxime proxetil (100 g, 0.1794 mol) in dichloro methane (700 mL) at -20 to -25 °C in 5-10 min. To the above solution was added N-methyl morpholine (54.2 g, 0.5366 mol) in dichloro methane (200 mL) and agitated till the HPLC analysis of the reaction mixture shown < 2.0 % of starting material, cefpodoxime proxetil. Water (300 mL) was added to reaction mixture, stirred and layers were separated. The organic layer was concentrated by distilling out dichloro methane under reduced pressure. The compound that obtained on concentration was diluted with toluene (500 mL). The diluted toluene solution was added to cyclohexane in 30 to 40 min to afford white solid of carbamate which on filtration, washing with cyclohexane (300 mL) and finally drying gave 110 g (95 %, molar) of carbamate of cefpodoxime proxetil.

Spectral data: IR (KBr, ν_{max}, cm^{-1}): 3277 (N-H *str.*), 1786, 1761, 1727, 1685; ^1H NMR ($CDCl_3$, 300 MHz, δ): 1.30-1.33 (m, 12H, $(CH_3)_2C$); 1.59 (d, J = 6 Hz, 3H, CH_3CH); 3.32 (s, 3H, OCH_3); 3.58 (s, 2H, H-1); 4.05 (s, 3H, N-OCH_3); 4.35 (s, 2H, CH_2O); 4.87-5.11 (m, 3H, H-6 and $CH(CH_3)_2$); 5.95-6.02 (m, 1H, H-7); 6.96 (q, J = 5.4 Hz, 1H, O-CH-O); 7.28 (s, 1H, Ar-H). MS (m/e): 644.

RESULTS AND DISCUSSION

The cefpodoxime proxetil is reacted with isopropyl chloroformate using N-methyl morpholine as base and in dichloromethane solvent. The reaction is carried out at -20 to -25 °C and after completion of the reaction, the reaction mixture is washed with water, separated the layers. The organic layer which consists the compound is concentrated and diluted with toluene. The solution is added to cyclohexane to isolate the title compound. The material is filtered, washed with cyclohexane and dried at 40 °C. The results are not satisfactory with other bases like N,N-dimethyl aniline, triethyl amine, DBU, DMAP, morpholine, Na_2CO_3 and pyridine. Also found in the study that excess of isopropyl chloroformate is required for completion of the reaction. The study is conducted with 3.5 mol of isopropyl chloroformate, 3.0 mol of NMM and the conversion is 97 % on HPLC.



Scheme: Preparation of carbamate of cefpodoxime proxetil

^{1}H NMR spectra of compound in $CDCl_3$ shows a multiplet (12 hydrogen) at 1.30-1.33 ppm due to presence of isopropyl groups and a multiplet (2 hydrogen) at 4.87-4.96 ppm due to -CH< confirms the carbamate functionality. Further the infrared spectrum shows -NH *str.* at 3277 cm^{-1}; -NH

bending at 1558 cm^{-1}; β-lactum C=O *str.* at 1761 cm^{-1}; C=O of amide *str.* 1681 cm^{-1}; alkyl > CH *str.* at 2985, 2940 confirms the compound. The mass spectra of the compound gives a prominent peak at m/z 644 amu $(M+H)^+$. Based on the spectral data, it is confirmed the title compound as carbamate of cefpodoxime proxetil.

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