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Process for Purification of 3-Alkenylcephem Carboxylic Acid†

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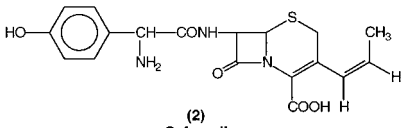
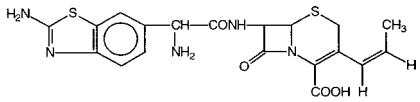
Abstract:
The present report describes a novel and efficient method for enrichment of 7-amino-3-[(*Z*)-propen-1-yl]-3-cephem-4-carboxylic acid (1) in a mixture of (*Z*/*E*) 7-amino-3[(*Z*/*E*)-propen-1-yl]-3-cephem-4-carboxylic acid via formation of 7-*β*-isopropylideneammonium salt in acidic conditions. This method provides high yield and 7-amino-3-[(*Z*)-propen-1-yl]-3-cephem-4-carboxylic acid (1) having a low *E*-isomer content from a mixture containing very high proportion of *E*-isomer. The usage of these isopropylidene ammonium salts provides a method for separation of mixtures of cephalosporins where geometric isomerism about a double bond exists.

Introduction

Cefprozil **(2)** and BMY 3522 **(3)** are highly effective broad-spectrum 3-propen-1-yl cephalosporin antibiotics. Synthetic processes for the production of these antibiotics generally yield mixtures containing both the *Z*- and *E*-isomers.



(2)
Cefprozil



(3)
BMY 3522

The *Z*- or cis-configuration of the propen-1-yl group is related to the activity of 3-propen-1-yl cephalosporin antibiotics against the Gram negative bacteria, hence the need to minimize the undesired *E*- or trans-isomer for optimum efficiency of these antibiotics. For example, the undesired *E*-isomer in Cefprozil should not exceed 11% according to U.S. Pharmacopoeia. 7-Amino-3-[(*Z*)-propen-1-yl]-3-cephem-4-carboxylic acid **(1)** is a key intermediate for preparation of above cephalosporin antibiotics. Synthetic methods for preparation of intermediate **1** are reported in the literature[1], which results in a mixture of *Z*- and *E*-isomers. In the preparation of intermediate **1**, the necessary olefination reaction may not progress selectively to the desired *Z*-isomer. In one of the literature methods[1b] intermediate **1** is produced with a maximum *Z*/*E* ratio of 90/10 or 91/9. Another method, as described in U.S. Patent 5,401,841, produces intermediate **1** containing *E*-isomer as high as 45−48%. Hence, further purification of this key intermediate **1** is necessary to achieve the required *Z*/*E* isomer ratio.

There are methods reported in the literature[2] for the enrichment of *Z*-isomer in intermediate **1** in a mixture of (*Z* and *E*)-7-amino-3-[(*Z*/*E*)-propen-1-yl]-3-cephem-4-carboxylic acid. In these methods, enrichment of *Z*-isomer in intermediate **1** is carried out via formation of hydrochloride salt, a metal or an amine salt or by adsorption chromatography. It has been observed that during purification via hydrochloride salt, the *Z*/*E* ratio of 85/15 produces *Z*/*E* ratio of 90/10 and also the filtration of the hygroscopic hydrochloride salts is difficult in commercial scale. Purification via formation of amine salt is also not very economical due to usage of amines such as dicyclohexylamine, octylamine, etc. Adsorption chromatography is also not commercially viable.

The present method gives highly efficient commercially viable method for enrichment of *Z*-isomer in intermediate **1** containing high levels of *E*-isomer. Levels as high as 30 to 35% can thus be reduced to accepted levels (7−8%) in a single step.

Results and Discussion

Cephalosporanic acid derivatives with a (cyclo) alkylidene ammonio groups are disclosed in the literature[3] and are used as a method of protecting an amino group wherein amino carboxylic acids have to be protected. Cephalosporanic acid derivatives with an aldimine substituent at the 7-position have been described for instance by W. A. Spitzer et al.[4] These compounds are therefore useful as synthetic intermediates. However, there has been no application of these isopropylideneammonium derivatives for the separation of mixtures of cephalosporins where geometric isomerism about a double bond exists. The present method provides a process for the enrichment of *Z*-isomer in intermediate **1** from a mixture of *Z*- and *E*-isomers in intermediate **1** via formation of isopropylidene ammonium salt **4** in acidic medium as outlined in Scheme 1.

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† A Patent Application (No. 1024/DEL/2002) incorporating parts of this report has been filed.

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(3) Neeft, J. M. I.; Verweij, J.; Hirs, H. G. J.; de Vroom, E. *Tetrahedron* **1996**, *52*, 11905.

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Scheme 1

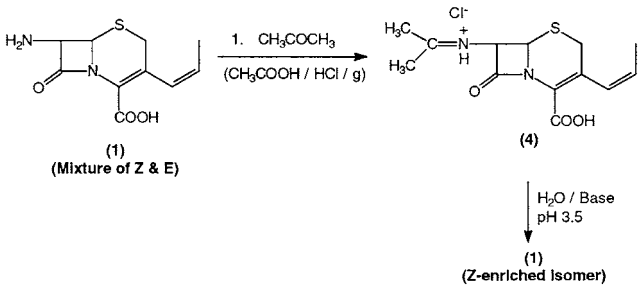

Table 1. **Intermediate 4 recoveries obtained on intermediate 1 samples possessing variable *Z*/*E* ratios, along with subsequent recoveries of purified intermediate 1 following intermediate 4 hydrolysis**

	intermediate **1**	intermediate **4**		intermediate **1** (purified)	
sample	*Z*/*E* ratio	*Z*/*E* ratio	recovery (%)	*Z*/*E* ratio	recovery (%)
1	80/20	92/8	84	92/8	80
2	88.5/11.5	93/7	88	93/7	80
3	85/15	93/7	88	93/7	80
4	75/25	92/8	80	93/7	78
5	70/30	90/10	75	92/8	78
6	51.5/48.5	82/18	73	83/17	53

A mixture containing *Z*- and *E*-isomers of intermediate **1** is dissolved in a mixture of acetone and acetic acid saturated with hydrochloric acid in substantially anhydrous medium to obtain *Z*-isomer-enriched isopropylidene ammonium salt **4** as depicted in Scheme 1. Further, intermediate **4** which possesses an improved *Z*/*E* ratio, is subsequently converted into intermediate **1** in conventional manner, e.g. by means of pH adjustment in water to its isoelectric point.

From Table 1, it is evident that this method is more efficient than the previously reported method[2] in reduction of *E*-isomer in intermediate **1** in good yield.[5] This process is simple and does not require any expensive raw materials.

Conclusions

The present method describes an efficient, simple and commercially viable process for reduction of *E*-isomer from a mixture of *Z*- and *E*-isomers of 7-amino-3-[(*Z*)-propen-1-yl]-3-cephem-4-carboxylic acid **(1)**.

Experimental Section

General. Starting material 7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid **(1)** was prepared by the reported procedure,[1c] and other reagents were used as such without further purification. HPLC was performed with a Waters' instrument using Hypersil ODS, 5 μm (250 m $\times$ 4−6 mm) column; ^{1}H NMR spectra were recorded using a Braker 300 MHz in TFA or $D_2O-Na_2CO_3$. The chemical shift data is reported as δ (ppm) downfield from tetramethylsilane which was used as an internal standard.

Preparation of (6*R*,7*R*)-7-Isopropylideneammonio-3-[*Z*/*E*)-propen-1-yl]-3-cephem-4-carboxylic acid hydrochloride (4). 7-Amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid **(1)** (100 g, *Z*/*E*: 80/20) was dissolved in a mixture of acetic acid (200 mL) and acetone (500 mL) saturated with hydrogen chloride gas (100 g) at 20−30 °C. After 5 min acetone (500 mL) was added, and a solid was separated from the clear solution. After stirring at 0−5 °C for 2−3 h, the titled product was filtered, washed with acetone, and dried to give 110 g (∼84%) isopropylideneammonium derivative **4**. *Z*/*E* Ratio: 92/8, ^{1}H NMR (CF_3COOD): 2.54 (d, 3H, $C\underline{H}_3$), 3.51 (s, 3H, $(C\underline{H}_3)_2C{=}N-$), 3.58 (s, 3H, $(C\underline{H}_3)_2C{=}N-$), 4.25−4.55 (m, 2H, $-SC\underline{H}_2-$), 6.30 (d, J = 4.2 Hz, 1H, β-lactam), 6.73−6.86 (m, 2H, $CH{=}C\underline{H}CH_3$ and β-lactam), 7.28−7.34 (d, J = 11.4 Hz,1H, $C\underline{H}{=}CHCH_3$). IR (KBr, cm^{-1}): 3426, 2906, 1780, 1707, 1653, 1621, 1404, 1351, 1213, 809, 718, and 691.

Regeneration of 7-Amino-3-[(*Z*/*E*)-propen-1-yl]-3-cephem-4 -carboxylic Acid (1) from 7-Isopropylidene-ammonium-3-[(*Z*/*E*)-propen-1-yl]-3-cephem-4-carboxylic acid hydrochloride(4). 7-Isopropylidene-ammonium-3-[(*Z*/*E*)-propen-1-yl]-3-cephem-4-carboxylic acid hydrochloride **(4)** (from above, 100 g *Z*/*E*: 92/8) was suspended in water (2000 mL) at room temperature (pH 0.5−0.7). The pH was adjusted with 1 N NaOH (∼550 mL) to 8.0−8.5 to obtain a clear solution. Activated carbon (10 g) was added and stirred for 15 min, filtered, and washed with water (200 mL). The pH of the filtrate was adjusted to 3.0−3.5 with 6 N hydrochloric acid. Solid so obtained was stirred for additional 30 min at room temperature and then filtered, washed with water followed by acetone. Drying at 48−50 °C resulted in 61 g (80%) of the titled product. *Z*/*E* Ratio: 92/8, *E*-content (by NMR): 8.0, Assay (by HPLC): 99.5%, ^{1}H NMR (D_2O/Na_2CO_3): 1.63 (d, 3H, $C\underline{H}_3$), 3.34−3.70 (ABq, J = 17.7 Hz, 2H, $SC\underline{H}_2$), 4.59 (d, J = 4.6 Hz, 1H, β-lactam), 4.92 (d, J = 4.6 Hz, 1H, β-lactam), 5.47−5.58 (m, 1H, $CH{=}C\underline{H}$-CH_3), 5.97 (d, J = 11.4 Hz, $C\underline{H}{=}CH-CH_3$).

(5) The reported methods in U.S. Patent 6,333,409 describes the reduction of *E*-isomer by HCl salt formation and dicyclohexylamine salt formation, and by adsorption chromatography using HP-20 resin. By these methods levels as high as 30−35% of *E*-isomer in 7-amino-3[(*Z*)-propen-1-yl]-3-cephem-4-carboxylic acid (**1**) cannot be reduced to the accepted levels of 7−8% in a single step.

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