

A CONVENIENT METHOD FOR THE ESTERIFICATION OF  
CEPHALOSPORANIC ACIDS

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Esterification of  $\Delta^3$ -cephalosporanic acid salts often presents problems associated with double bond isomerization resulting in a mixture of the  $\Delta^3$ -ester and the  $\Delta^2$ -ester.<sup>1)</sup> The desired  $\Delta^3$ -cephem isomers must be isolated by fractional crystallization or elution chromatography and  $\Delta^2$ -esters can be converted to the  $\Delta^3$ -esters via the sulphoxide.<sup>2)</sup> And so, an efficient and simple procedure for preparation of  $\Delta^3$ -esters is clearly desirable. In this communication we wish to report a new method for preparing  $\Delta^3$ -ester without isomerization. Thus we used liquid sulphur dioxide as solvent for esterification of  $\Delta^3$ -cephalosporanic acid salts with activated alkyl halides and obtained  $\Delta^3$ -esters in good yield.

To a solution of cephalosporanic acid and triethylamine in liquid sulphur dioxide, 1.2~2.0 eq. of alkyl halide was added and refluxed for 2~5 hrs. The products in high yield were identified to  $\Delta^3$ -esters and probed to be free of  $\Delta^2$ -esters by a comparison with authentic samples. (TLC and NMR) The results are summarized in the table.

It is known that the cephem double bond is isomerized by cephem carboxylic acid salt itself or base.<sup>1), 3)</sup> When excess bases and cephalosporanic acid anions are never present in the esterification mixture (ex. in DMF solution) the products are largely free of any  $\Delta^2$ -isomers.<sup>3)</sup>

In liquid sulphur dioxide, we assumed, the base and acid anion are strongly solvated<sup>4)</sup> and so do not cause isomerization of the double bond. When dichloromethane solutions of the pure  $\Delta^3$ -esters were stirred at  $-10^\circ\text{C}$  with two equivalents of base such as triethylamine, 4-dimethylaminopyridine or DBN,  $\Delta^2$ - $\Delta^3$  equilibrium mixtures were obtained, respectively. In liquid sulphur dioxide, on the other hand, isomerization did not occur with these bases. It is noteworthy that in dichloromethane esterification of acid salts with alkyl halides did not proceed after a day and when the equivalent

volume of liquid sulphur dioxide was added in the solution the reaction started immediately.

It seems that such strong ionizing power,<sup>5)</sup> highly selective solvation, high solubility of organic compounds and broad liquid range (b.p.  $-10^{\circ}\text{C} \sim$  m.p.  $-75.5^{\circ}\text{C}$ )<sup>4)</sup> make sulphur dioxide suitable solvent for use of esterification of cephalosporanic acids.

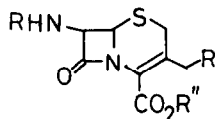
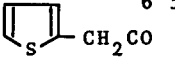


Table  $\Delta^3$ -Cephalosporanic Acid Esters<sup>6)</sup>

No	R	R'	R''X (halide)	Yield%	m.p. °C
1	$\text{HO}_2\text{C}\cdot\underset{\text{NHCOC}_6\text{H}_5}{\text{CH}}(\text{CH}_2)_3\text{CO}$	OAc	$(\text{C}_6\text{H}_5)_2\text{CHCl}$	*85	173-175
2	 $\text{CH}_2\text{CO}$	OAc	$(\text{C}_6\text{H}_5)_2\text{CHCl}$	89	142-143
3			$p\text{-CH}_3\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Cl}$	59	150-151
4			$p\text{-O}_2\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Br}$	47	154-156
5			$\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$	74	177
6			$\text{CH}_3\text{CO}_2\text{CH}_2\text{Br}$	60	144-145
7			$\text{CH}_3\text{CO}_2\text{CH}_2\text{I}$	84	
8	$\text{C}_6\text{H}_5\text{OCH}_2\text{CO}$	H	$(\text{C}_6\text{H}_5)_3\text{CCl}$	68	181
9			$\text{CH}_3\text{OCH}_2\text{Cl}$	98	110-111
10			$\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$	82	171

\* di-ester

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- 6) All compounds had satisfactory analytical and spectroscopic data.