7α-HYDROXYCEPHALOSPORIN C, AN INTERMEDIATE IN THE METHOXYLATION OF CEPHALOSPORIN C BY A CELL-FREE EXTRACT OF S. CLAVULIGERUS

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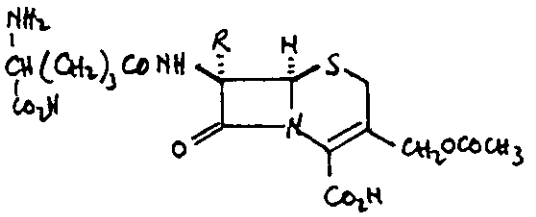
One of the β-lactam antibiotics produced by Streptomyces clavuligerus is cephamycin C (1). Abraham and co-workers have reported [1] that cell-free extracts of S. clavuligerus convert cephalosporin C (2) and the O-carbamoyl analogue (3) into the corresponding cephamycins (4) and (1). It was suggested that methoxylation was a two stage process involving molecular oxygen and a methyl transfer from methionine. [1,2]

A detailed examination of this methoxylation stage in cephamycin biosynthesis has been undertaken. Cephalosporin C (2) was incubated with a cell free preparation from S. clavuligerus, and h.p.l.c. analysis indicated the formation of 7α-hydroxycephalosporin (5) together with 7α-methoxycephalosporin C (4); (5) was isolated and fully characterised spectroscopically and by comparison with synthetic material. 7α-hydroxycephalosporin C (5) was treated in a similar manner with the same enzyme preparation including added S-adenosylmethionine and 7α-methoxycephalosporin C (4) detected by h.p.l.c.

This evidence confirms that the methoxylation of cephalosporin C is a two stage process, oxygenation of the cephalosporin yielding a 7α-OH intermediate which is subsequently methylated.



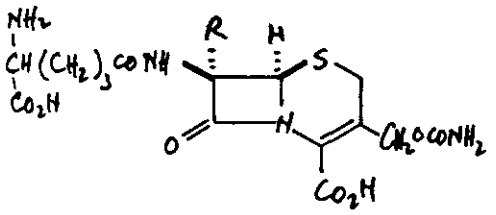
(2) R = H

(4) R = OMe

(5) R = OH

(1) R = OMe

(3) R = H



1. Biochem. J., 1979, 179, 47; 1980, 186, 613.

2. Antimicrob. Agents. Chemother., 1972, 1, 247.