A New Synthetic Route to 7α-Methoxycephalosporins

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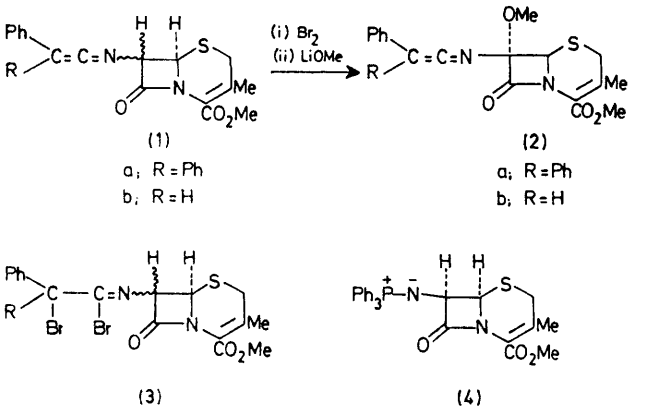
Summary 7α-Methoxy-7β-acetamidocephalosporin derivatives were synthesized from 7-vinylidenamino-cephalosporins *via* 7α-methoxy-7β-vinylidenamino-derivatives.

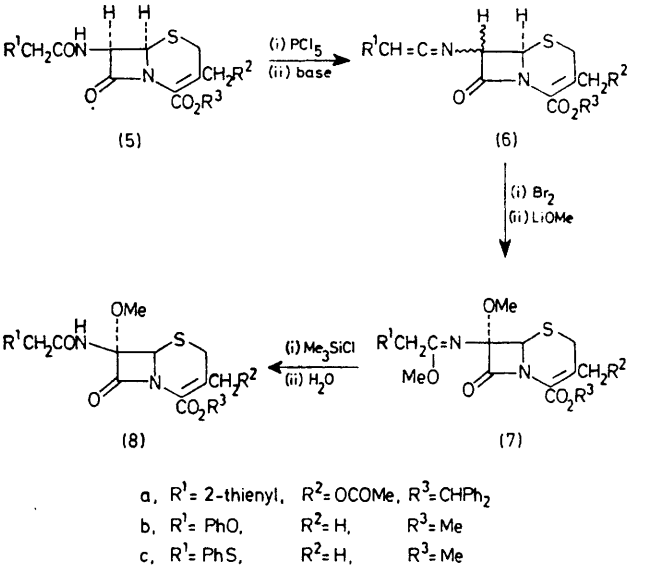
WE have recently reported a novel synthesis of 7-methoxycephalosporins and 6-methoxypenicillins,[1] the key step of which was production of a 7- (or 6-) imino-cephalosporin (penicillin) intermediate *via* 1,4-elimination. We report here another route to 7α-methoxycephalosporin derivatives starting from 7-acetamido cephalosporin derivatives. Treatment of the vinylidenamine (**1a**) in tetrahydrofuran with slight excess of bromine[2] at −20 to −30 °C and subsequently with a methanolic solution of LiOMe at −78 °C gave the 7α-methoxy-7β-vinylidenamino-derivative (**2a**) in 55% yield. Analogously, the 7α-methoxy-7β-vinylidenamino-compound (**2b**) was obtained from (**1b**), which was prepared from methyl 7β-phenylacetamido-3-methylceph-3-em-4-carboxylate according to a known method.[3] The vinylidenamines (**2**) could be purified by silica gel chromatography without hydrolysis and were easily identified by their characteristic i.r. band at 2000 cm^{-1}. It should be noted that bromine attacked the vinylidenamine part of compounds (**1**) in preference to the 1 or 2 position of the cephem skeleton to give the intermediate (**3**).[4] The vinylidenamine (**2b**) was converted into

the corresponding amide quantitatively on treatment with trifluoroacetic acid at room temperature.



Depending on the type of substituent on the vinylidenamine unit, an imino-ether may be isolated during the methoxylation. Thus, a solution in tetrahydrofuran of the imino-chloride which was obtained from the ester (**5a**) and PCl_5–quinoline, was treated with triethylamine for 15 min at room temperature to afford the vinylidenamine (**6a**). Without isolation (**6a**) was brominated at −50 °C, and excess of lithium methoxide in methanol was added at −78 °C to give the imino-ether (**7a**) in 49% yield after silica gel chromatography; ν_{max} (liquid) 1780, 1740, and 1650 cm^{-1}, δ ($CDCl_3$) 1·96 (3H, s), 3·28 and 3·45 (2H, AB q, *J* 18 Hz), 3·34 (3H, s), 3·69 (3H, s), 3·93 and 4·20 (2H, AB q, *J* 14 Hz), 4·62 and 4·90 (2H, AB q, *J* 14 Hz), 4·97 (1H, s), 6·90 (1H, s), 6·8—7·0 (2H, m), and 7·0—7·5 (11H, m). Treatment of the imino-ether (**7a**) with Me_3ClSi in $CHCl_3$ overnight at room temperature gave the 7α-methoxy-ester (**8a**) in 50% yield; i.r. and n.m.r. data similar to those for (**7a**). Analogously (**5b**) and (**5c**) furnished the 7α-methoxy-imino-ethers (**7b**) and (**7c**), respectively.

The 7β-acetamido cephalosporin derivatives could thus be converted into 7α-methoxy-7β-acetamidocephalosporin derivatives by these reactions without any change in the 7β-side chain *via* the imino-ethers (**7**) or the vinylidenamines (**2**).



a, R^1 = 2-thienyl, R^2 = OCOMe, R^3 = $CHPh_2$
b, R^1 = PhO, R^2 = H, R^3 = Me
c, R^1 = PhS, R^2 = H, R^3 = Me

The vinylidenamine (**1a**) could also be prepared from the phosphorus ylide (**4**)[5] and $Ph_2C{=}C{=}O$. However, this reaction seems to be limited to isolable ketens such as $Ph_2C{=}C{=}O$.

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[3] R. D. Carroll, E. S. Hamanaka, D. K. Pirie, and W. M. Welch, *Tetrahedron Letters*, 1974, 1515.
[4] D. O. Spry, *Tetrahedron Letters*, 1972, 3717.
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