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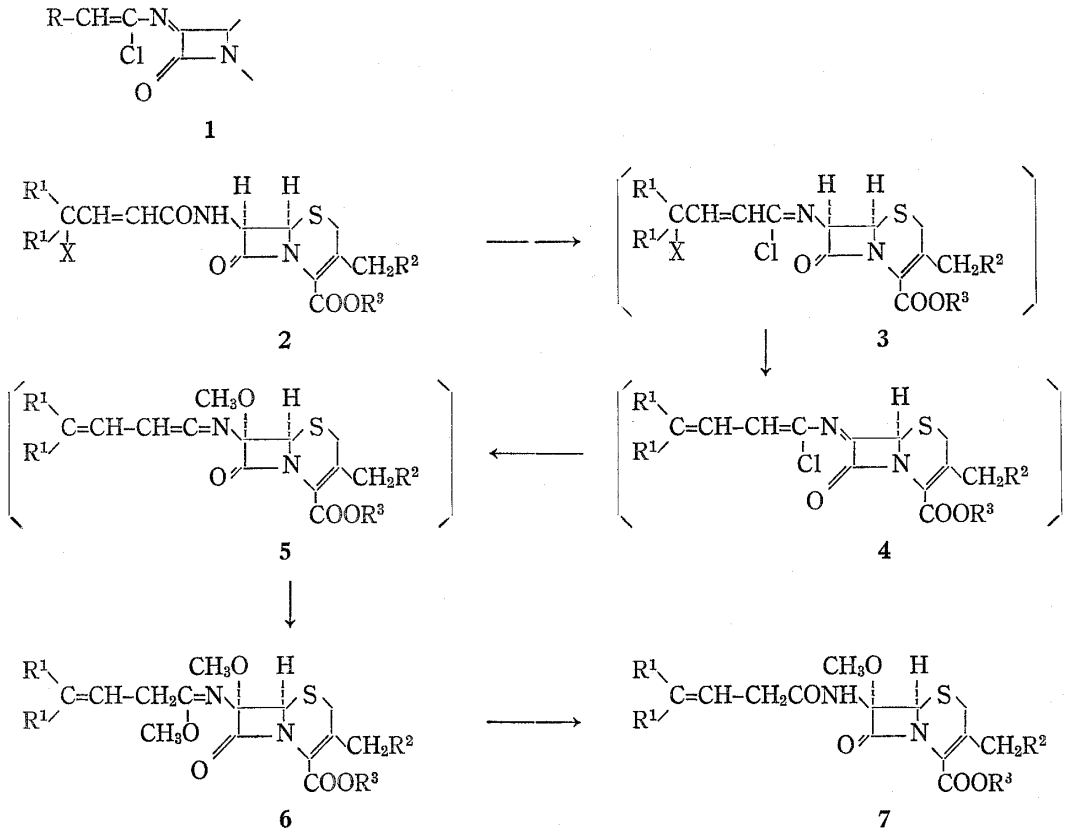
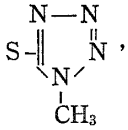
7α-Methoxylation of Cephalosporins

7α-Methoxy-7β-vinylacetamidocephalosporins were synthesized from 7β-(ω-halocrotonyl)aminocephalosporins using phosphorus pentachloride and lithium methoxide by a 1,6-elimination reaction.

Keywords——cephalosporin; 7α-methoxycephalosporin; methoxylation; 1,6-elimination; trimethylchlorosilane

The finding of natural 7α-methoxycephalosporins[1] and the enhanced antibacterial activity of their modified analogues[2] have stimulated the search for a convenient method for introduc-



a: R^1=Cl, R^2=$OCOCH_3$, R^3=$CHPh_2$, for **2** and **3** X=Cl
b: R^1=Cl, R^2=H, R^3=*t*-Bu, for **2** and **3** X=Cl
c: R^1=H, R^2=H, R^3=CH_3, for **2** and **3** X=Br
d: R^1=Cl, R^2=  , R^3=H, for **2** and **3** X=Cl

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2) *a*) P.P.K. Ho, R.D. Towner, J.M. Indelicato, W.J. Wilham, W.A. Spitzer, and G.A. Koppel, *J. Antibiotics* (Tokyo), **26**, 313 (1973); *b*) H. Nakao, H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara, *J. Antibiotics* (Tokyo), **29**, 554 (1976).

ing a methoxy group at the 7α-position of cephalosporins.[3] Recently we have disclosed[4] new methods for preparation of 7α-methoxycephalosporins through a halogenoimine (**1**) by a 1,4-elimination of hydrogen halide from a haloimino chloride. Now we wish to report the formation of the imine (**1**) by a 1,6-elimination which leads to a stereospecific 7α-methoxylation. This exemplifies a wide applicability and extension of our original method[4a] to methoxylation at the 3-position of 2-azetidinone system.

A tetrahydrofuran solution of the imino chloride (**3a**), which was obtained from 7β-(ω,ω,ω-trichlorocrotonyl)amino-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (**2a**) and PCl_5–quinoline, was treated with a methanolic solution of lithium methoxide at −70° for 20 min to give the imino ether (**6a**) in 75% yield, **6a**: NMR ($CDCl_3$) δ ppm 1.95 (3H, s), 3.20 and 3.50 (2H, AB-q, J=18 Hz), 3.42 (3H, s), 3.72 (3H, s), 3.5—3.9 (2H), 4.67 and 4.92 (2H, AB-q, J=13 Hz), 4.97 (1H, s), 5.98 (1H, t, J=7 Hz), 6.94 (1H, s) and 7.0—7.6 (10H). The imino ether (**6a**), on treatment with trimethylchlorosilane and quinoline in chloroform at room temperature for 3 hours, afforded 7α-methoxy-7β-(2,2-dichlorovinyl)acetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (**7a**) in 90% yield, **7a**: NMR ($CDCl_3$) δ ppm 1.92 (3H, s), 3.0—3.8 (2H+2H), 3.48 (3H, s), 4.75 and 4.95 (2H, AB-q, J=13 Hz), 5.05 (1H, s), 6.00 (1H, t, J=6 Hz), 6.90 (1H, s) and 7.0—7.7 (10 H).

Analogously **2b** and **2c** afforded the corresponding imino ethers **6b** and **6c** in 60% and 27% yield, respectively.

In the case of **2d** the 4-carboxylic group was first protected as trimethylsilyl ester and successive treatment with PCl_5–quinoline at −50° and with a methanolic solution of lithium methoxide at −70° in chloroform gave the imino ether (**6d**). This imino ether (**6d**), without prior purification, was converted to the corresponding amide (**7d**) with trimethylchlorosilane in 35% yield from **2d**, 7d: NMR (CD_3COCD_3) δ ppm 3.20 and 3.55 (2H, AB-q, J=18 Hz), 3.50 (3H, s), 3.67 (2H, d, J=7 Hz), 4.00 (3H, s), 4.40 (2H, s), 5.04 (1H, s) and 6.16 (1H, t, J=7 Hz).

Consequently, the formation of an exo-imine of a β-lactam and the resulting 7α-methoxylation of cephalosporins were realized *via* 1,6-elimination of HX with lithium methoxide in addition to already reported 1,4-elimination schemes.[4]

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3) For methods of preparation of 7α-methoxycephalosporins, see references cited in 4*a*).
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