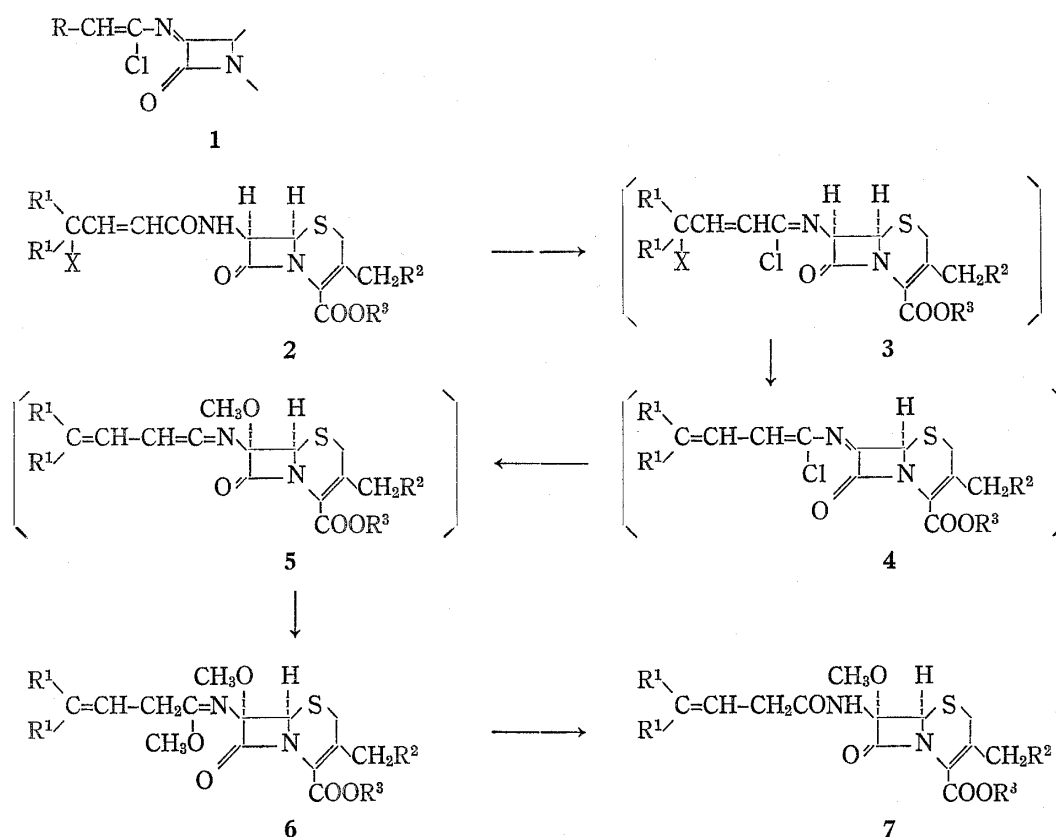


7 α -Methoxylation of Cephalosporins

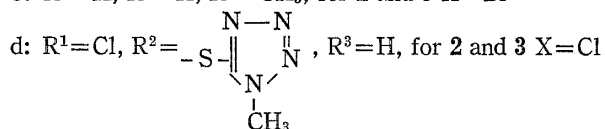
7 α -Methoxy-7 β -vinylacetamidocephalosporins were synthesized from 7 β -(ω -halocrotonyl)aminocephalosporins using phosphorus pentachloride and lithium methoxide by a 1,6-elimination reaction.

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

The finding of natural 7 α -methoxycephalosporins¹⁾ and the enhanced antibacterial activity of their modified analogues²⁾ have stimulated the search for a convenient method for introduc-



- a: R¹=Cl, R²=OCOCH₃, R³=CHPh₂, for **2** and **3** X=Cl
 b: R¹=Cl, R²=H, R³=*t*-Bu, for **2** and **3** X=Cl
 c: R¹=H, R²=H, R³=CH₃, for **2** and **3** X=Br



- 1) a) R. Nagarajan, L.D. Boeck, M. Gorman, R.L. Hamill, C.E. Higgins, M.M. Hoehn, W.M. Stark, and J.G. Whitney, *J. Am. Chem. Soc.*, **93**, 2308 (1971); b) E.O. Stapley, M. Jackson, S. Hernandez, S.B. Zimmerman, S.A. Currie, S. Mochales, J.M. Mata, H.B. Woodruff, and D. Hendlin, *Antimicrobial Agents and Chemotherapy*, **2**, 122 (1972); c) T.W. Miller, R.T. Goegelman, R.G. Weston, I. Putter, and F.J. Wolf, *ibid.*, **2**, 132 (1972).
- 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 7 α -position of cephalosporins.³⁾ Recently we have disclosed⁴⁾ new methods for preparation of 7 α -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 7 α -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 7 β -(ω,ω,ω -trichlorocrotonyl)amino-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (**2a**) and PCl₅-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 (CDCl₃) 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 7 α -methoxy-7 β -(2,2-dichlorovinyl)acetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (**7a**) in 90% yield, **7a**: NMR (CDCl₃) 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 PCl₅-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 (CD₃COCD₃) 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 7 α -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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Central Research Laboratories,
Sankyo Co., Ltd.,
1-2-58, Hiromachi, Shinagawa-ku,
Tokyo, 140, Japan

YUKIO SUGIMURA
KIMIO IINO
YUJI IWANO
TOKIO SAITO
TETSUO HIRAOKA

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

4) a) Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, *Tetrahedron Letters*, **1976**, 1307; b) T. Saito, Y. Sugimura, Y. Iwano, K. Iino, and T. Hiraoka, *Chem. Commun.*, **1976**, 516.