

Cleavage of the Aminoacidoyl Side Chain of Cephamycin C to the (6*R*, 7*S*)-7-Amino-7-methoxy Derivative

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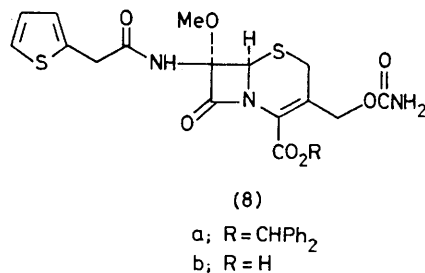
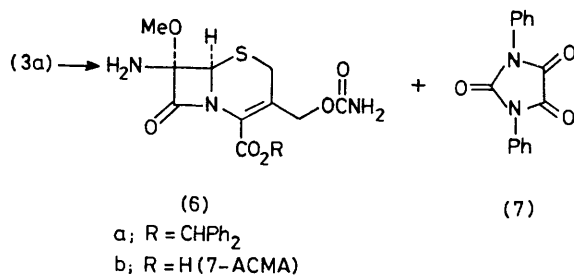
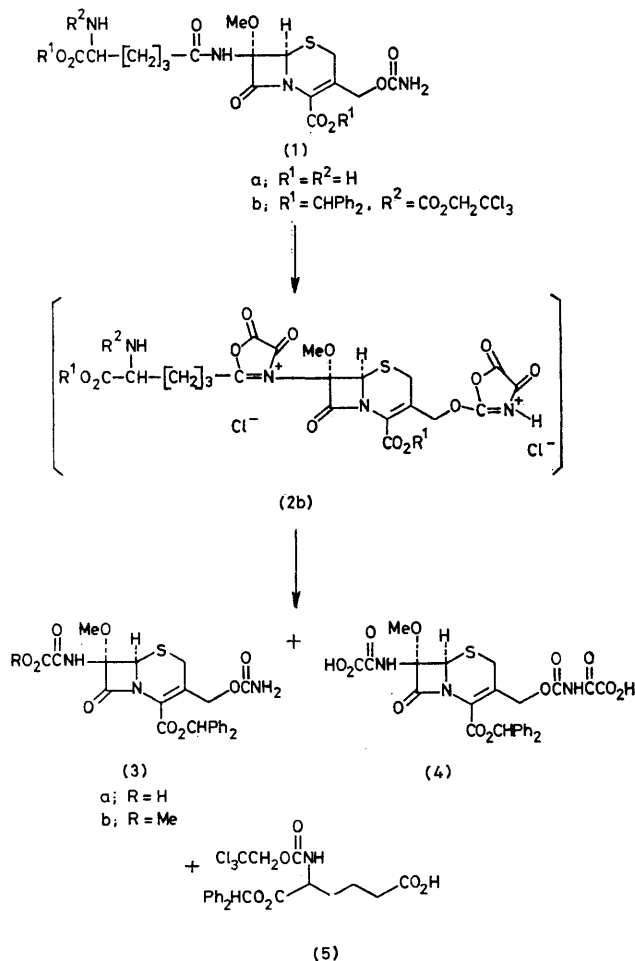
Summary (6*R*,7*S*)-Benzhydryl 7-amino-7-methoxy-3-carbamoyloxymethylceph-3-em-4-carboxylate (**6a**), which is an important intermediate for the synthesis of various analogues with a wide spectrum of antibiotic activity, has been obtained from cephamycin C (**1a**) via the oxamic acid intermediate (**3a**).

CONVERSION of naturally occurring cephamycin C (**1a**)¹ into a (7*S*)-7-amino-7-methoxy derivative (7-ACMA ester) by application of the phosphorus pentachloride method which is well established in the penicillin and cephalosporin fields,² is difficult, owing to formation of a strong phosphorus-nitrogen bond by the reaction of phosphorus pentachloride with the carbamoyloxy group of cephamycin C.³ We

report here the isolation of the 7-ACMA ester (**6a**) by a modification of our recently reported method.⁴

The *N*-protected cephamycin C dibenzhydryl ester (**1b**) was treated with 6 mol equiv. each of oxalyl chloride and anhydrous sodium carbonate in dry dioxan (20 °C; 15 h); the mixture was then quenched with water adjusted to pH 6–7 with aq. NaHCO₃, stirred (20 °C; 30 min), acidified to pH 2.0, extracted with ethyl acetate, and column chromatography on silica gel (15% water impregnated) gave the oxamic acid (**3a**) (37% yield), the dioxamic acid (**4**) (34%), and the aminoacidic acid derivative (**5**) (85%), m.p. 113–115 °C; *m/e* 501 (*M*⁺). We assume that (**2b**) is an intermediate in this reaction, the two oxazolimidone units of which result in different functional groups in the product. Treatment of (**4**) with acetone–water–conc. hydrochloric acid (10:5:1) (20 °C; 3 days) gave (**3a**) in 87% yield, whereas treatment of (**4**) with methanol–conc. hydrochloric acid (50:1) (25 °C; 18 h) afforded (**3b**) in 84% yield.

Reaction of the oxamic acid (**3a**) with 1.1 equiv. of diphenylcarbodi-imide in methylene chloride (5 °C; 16 h), followed by rapid thin layer chromatography (t.l.c.)† on silica gel produced the (6*R*,7*S*)-cephemcarboxylate (**6a**) and



the trione (**7**), m.p. 204 °C, in 56 and 72% yield, respectively. Neither double bond isomerization⁵ nor epimerization⁶ at chiral centres occurred under these conditions. For identification, (**6a**) was converted into (**8a**) with thiophen-2-acetyl chloride and *NN*-dimethylaniline. Treatment of the ester (**8a**) with trifluoroacetic acid in anisole yielded

† Chromatography of (**6a**) should be carried out as quickly as possible, otherwise some decomposition occurs.

cefodoxitin (**8b**), identical in all respects with an authentic sample.⁷ The analogous reaction of (**3a**) with diphenylcarbodi-imide (5 °C; 1 h), followed by addition of thiophen-2-acetyl chloride and *NN*-dimethylaniline, stirring (25 °C; 20 h), and separation by t.l.c. on silica gel, afforded (**8a**) in 31% yield without isolation of (**6a**).

This is the first practical method for formation of the 7-ACMA ester from cephamycin C, and we believe that its usefulness should be comparable to that of 7-ACA itself.

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¹ R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehm, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, 1971, **93**, 2308; E. O. Stapley, M. Jackson, S. Helnandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, *Antimicrobial Agents and Chemotherapy*, 1972, **2**, 112.

² E. H. Flynn, ed., 'Cephalosporins and Penicillins,' Academic Press, New York, 1972, pp. 47-55.

³ Y. Sugimura, T. Saito, and T. Hiraoka, unpublished work; S. Karady, L. M. Weinstock, F. E. Roberts, J. ten Broeke, R. F. Shuman, A. M. Hoinowski, S. H. Pines, and M. Sletzing, *Tetrahedron Letters*, 1976, 2401.

⁴ M. Shiozaki, N. Ishida, K. Iino, and T. Hiraoka, *Tetrahedron Letters*, 1977, 4059.

⁵ Cf., S. Karady, J. S. Amato, L. M. Weinstock, and M. Sletzing, *Tetrahedron Letters*, 1978, 407.

⁶ Cf., W. H. W. Lunn, R. W. Burchfield, T. K. Elzey, and E. V. Mason, *Tetrahedron Letters*, 1974, 1307.

⁷ Prepared from (**1b**) by the known method by the use of molecular sieves: L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, and M. Sletzing, *Tetrahedron Letters*, 1975, 3979.