Cleavage of the Aminoadipoyl 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. $NaHCO_3$, 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 aminoadipic 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 oxazolidinedione 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 isomerization[5] nor epimerization[6] 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

(1)
a; $R^1 = R^2 = H$
b; $R^1 = CHPh_2$, $R^2 = CO_2CH_2CCl_3$

(2b)

(3)
a; R = H
b; R = Me

(4)

(5)

(6)
a; $R = CHPh_2$
b; R = H (7-ACMA)

(7)

(8)
a; $R = CHPh_2$
b; R = H

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

cefoxitin (**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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