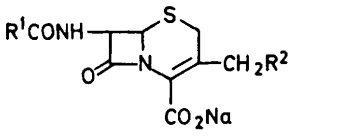
Reduction of Cephalosporanic Acids with Chromium(II) Salts: Synthesis of 3-Methylenecepham Derivatives

By M. OCHIAI,* O. AKI, A. MORIMOTO, T. OKADA, and H. SHIMADZU
(*Central Research Division, Takeda Chemical Industries, Ltd., Juso, Osaka, Japan*)

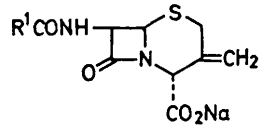
Summary Cephalosporanic acid derivatives (I) were converted into 3-methylenecepham derivatives (II) on treatment with chromium(II) salts in aqueous media, and esters of 3-methylenecepham derivatives were readily isomerized to the 3-methyl-3-cephem derivatives (VII) under basic conditions.

CHEMICAL modification of cephalosporanic acid derivatives requires mild reaction conditions due to the presence of the labile β-lactam structure in the molecule. We now report a new and convenient synthesis of 3-methylenecepham derivatives, a novel class of cephalosporins, by the reduction of cephalosporanic acids with chromium(II) salts.

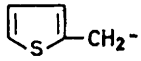
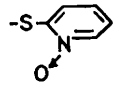
When sodium 7-(2-thienylacetamido)cephalosporanate (6·72 g) (Ia) was treated with chromium(II) acetate (8·00 g)[1] in H_2O–Me_2SO (400 ml, 1 : 1) at room temperature in an atmosphere of nitrogen for 24 h, the 3-methylenecepham compound (IIa) was obtained (44%), m.p. 208—212 °C

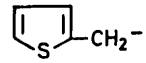


(I)

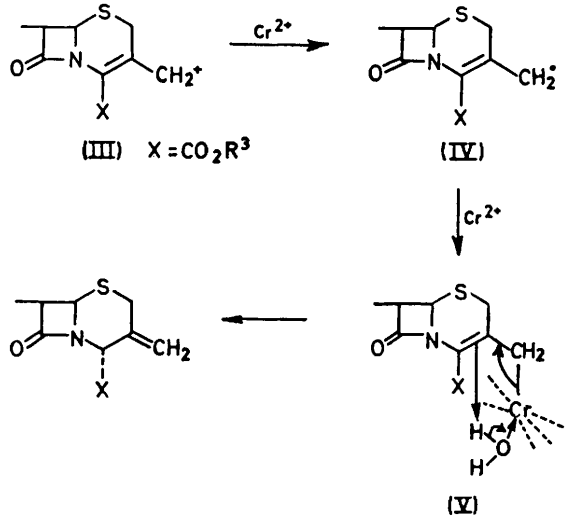


(III)

	R^1	R^2
a;		OAc
b;	"	SAc
c;	"	SBz
d;	"	
e;	$PhCH_2$-	OAc
f;	$PhOCH_2$-	OAc

	R^1
a;	
e;	$PhCH_2$-
f;	$PhOCH_2$-

(decomp.). I.r. and n.m.r. data and elemental analysis are in agreement with the 3-methylenecepham structure (IIa). The stereochemistry of the 4-carboxy-group was shown to be α on the basis of an n.m.r. study. Details of this will be reported elsewhere.



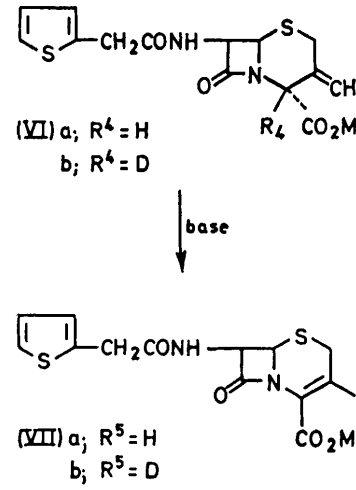
(III) X = CO_2R^3 (IV) (V)

SCHEME

When the reaction was conducted in a non-aqueous solvent or with the methyl ester of (Ia) in aqueous media the starting material was recovered unchanged. Thus it is likely that the reaction proceeds through the initial formation of a carbonium ion (III)[2] followed by reduction with chromium(II) ion and subsequent formation of the complex (V) (see Scheme).[3]

Chromium(II) sulphate[4] and chloride[5] were also effective in the present reaction but less satisfactorily. Other cephalosporins such as (Ib), (Ic), and (Id)[6] also gave (IIa). (Ie) and (If) led to the corresponding 3-methylenecepham derivatives (IIe, IIf).

The methyl ester (VIa) was isomerized to the 3-methylcephem derivative (VIIa) under basic conditions. Thus the treatment of (VIa) (35 mg) with pyridine (0·4 ml) at room temperature for 24 h gave the 3-methylcephem derivative (VIIa) quantitatively. (VIIa) was shown to be identical with the methyl ester of 7-(2-thienylacetamido)-3-deacetoxy cephalosporanic acid obtained by the acylation of 7-amino-3-deacetoxycephalosporanic acid with 2-thienylacetyl chloride.[7]



(VI) a; R^4 = H
b; R^4 = D

(VII) a; R^5 = H
b; R^5 = D

The 4-deuteriated 3-methylenecepham derivative (IIa; 4-D) was obtained by the treatment of (Ia) with chromium(II) acetate in D_2O and was converted into the methyl ester (VIb) by treatment with diazomethane. The ester (VIb) was isomerized in pyridine to the 3-methylcephem derivative (VIIb). The same compound (VIIb) was obtained when (VIa) was treated with pyridine containing a small amount of D_2O.

Neither (IIa), (IIe), nor (IIf) had significant antibacterial activity.

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