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A NOVEL SIMPLE SYNTHESIS OF 7α-SUBSTITUTED CEPHALOSPORINS

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Recently a number of laboratories[1] have reported methods for the introduction of the methoxy group into cephalosporin at C-7 since the discovery of cephamycins which have strong antimicrobial activity. In order to find new potent substances several derivatives other than methoxy derivative have been synthesized, i.e., alkyl, acyl or carboxyl derivatives[2] prepared from the alkyl, acyl or alkoxycarbonyl halides and the Schiff base of 7-aminocephalosporanic acid ester, methylthio derivatives[3] prepared by methylthiolation of the Schiff base, and others[4] However there has been no general simple method to introduce substituents into cephalosporin at C-7 via nucleophilic attack. In a previous paper[5] we reported the facile synthesis of 7α-methoxycephalosporin, that is, the methoxy group was introduced into cephalosporin at C-7 by addition of methanol to the reactive quinoidal compound (II) prepared from Schiff base (I) by oxidation with PbO_2. In addition, this procedure, namely addition of nucleophile to II, has led to the successful synthesis of many sorts of 7α-substituted derivatives which we would like to report at this time.

The reaction of an alcohol such as ethanol, propanol, cyanomethanol and methyl cellosolve with II in a benzene solution at room temperature proceeded in the same manner as with methanol[5] to yield the corresponding, new 7α-ethoxy, propoxy, cyanomethoxy and 2-methoxyethoxy derivatives (IIIa-d), respectively. Addition of a mercaptan e. g. a solution of methyl mercaptan in diethyl ether to a benzene solution of II gave the 7α-methylthio analogue (IIIe). Moreover, the reaction of compounds having an active proton such as hydrogen cyanide, ethyl malonate or hydrazoic acid with II also afforded the corresponding 7α-substituted Schiff base (IIIf-h), respectively. These

products (III) were purified by silica gel column chromatography with the solvent system of benzene - ethyl acetate. Yields and NMR data are shown in Table 1 Treatment of III with Girard T reagent in methanol by similar procedures described in a previous paper[5] gave the corresponding amine (IV) except IIIh which afforded the 7α-methoxy derivative by methanolysis of azido group Acylation of IV with thienylacetyl chloride followed by removal of diphenylmethyl group with trifluoroacetic acid afforded the corresponding 7α-substituted cephalosporin (V) whose yields from III and NMR data are shown in Table 2. The substituents of V are assigned the 7α-configuration by analogy with examples in a previous paper[5]. These compounds showed weak antimicrobial activities Details will be published elsewhere.

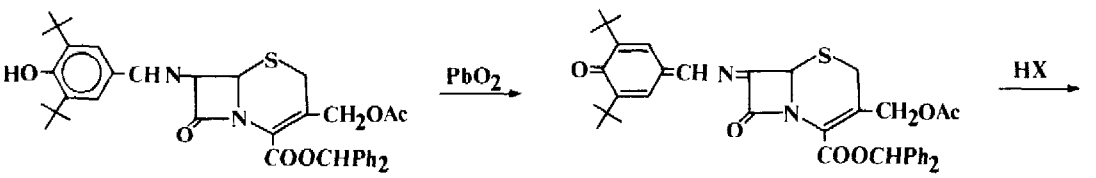
Table 1. Yields and NMR data of III

	Yield(%)	NMR (δ in $CDCl_3$)		
	from I	CH=N	C_6-H	X
IIIa	71	8.51	5.04	1.25(CH_3,t,J=7) 3.76(OCH_2,q,J=7)
IIIb	65	8.41	4.96	0 88(CH_3,br t,J=6) 1.70(C-CH_2-C,m) 3.58(OCH_2,br t,J=6)
IIIc	47	8.40	5.11	4.50(CH_2,s)
IIId	51	8.42	5.00	3.26(CH_3,s) 3.55, 3.80(CH_2-CH_2,A_2B_2)
IIIe	45	8 58	4.98	2 20(CH_3,s)
IIIf	42	8.46	5.24	-
IIIg	52	8.60	5.53	1.20, 1.27(CH_3,t,J=7) 3.93(CH,s) 4 13, 4.28(OCH_2,t,J=7)
IIIh	49	8 57	5.00	-

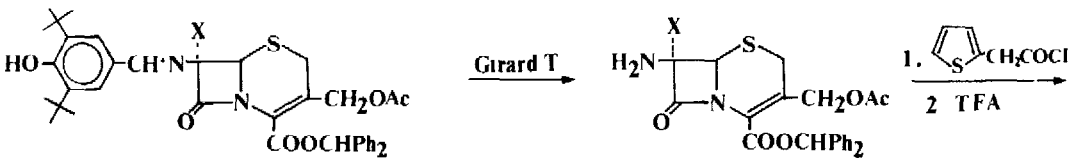
Table 2. Yields and NMR data of V

	Yield(%) from III	NMR (δ in DMSO-d_6) C_6-H	X
Va	58	5.09	1.10(CH_3,t,J=7) 3.67(CH_2,q,J=7)
Vb	39	5 10	0.80(CH_3,t,J=7) 1.41(C-CH_2-C,m) 3.55(OCH_2,t,J=7)
Vc	21	5.15*2	4.61(CH_2,s)
Vd	70	5.12	3 20(CH_3,s) 3,4, 3.7(CH_2-CH_2,A_2B_2)
Ve*1	65	4.99	2.20(CH_3,s)
Vf	14	5.24	-
Vg	33	5.10*3	1.22(CH_3,t,J=7) 4.20(CH_2,q,J=7) 4 64(CH,s)

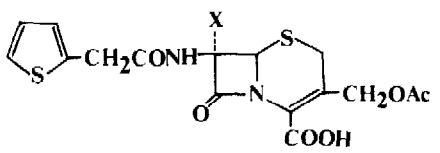
*1) mp 141-142° *2) in CD_3COCD_3 *3) in $CDCl_3$



I II



III IV



V

a, $X=OC_2H_5$ b, $X=OCH_2CH_2CH_3$

c, $X=OCH_2CN$ d, $X=OCH_2CH_2OCH_3$

e, $X=SCH_3$ f, $X=CN$

g, $X=CH(COOC_2H_5)_2$ h, $X=N_3$

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3. These are intermediates to 7-methoxycephalosporin. See 1c, 1d and 1e.

4. (a) Acetoxy derivative: W A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S Puar, M. Young and J. E. Dolfini, J Org Chem., 38, 943 (1973). (b) Alkoxy derivative: G A. Koppel and R E. Koehler, Tetrahedron Lett , 1943 (1973). (c) Hydroxy derivative: W A. Spitzer, T Goodson Jr., M O Chaney and N. D Jones, ibid., 4311 (1974) (e) Ethoxyformamido derivative: M. M Campbell and G. Johnson, Chem Commun., 479 (1975).

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