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SYNTHESIS OF 7α-SUBSTITUTED CEPHALOSPORINS PART III[1)]

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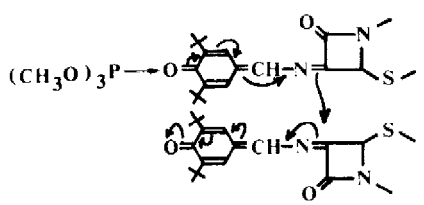
Modification of C-7 position in cephalosporin is one of the most important aspects in the chemistry of β-lactam antibiotics in the search for new potent antibiotics since Strominger's hypotheses[2)] and the discovery of cephamycins[3)]. Previously we announced the quinoid (I) as the key intermediate in the synthese of 7α-methoxy and other 7α-substituted cephalosporins[1)]. We have been studying the reactivity of I and now we present the reaction of I with trimethyl phospite to afford 7α,7α'-dimeric and 7α-dimethylphosphono cephalosporins[4)].

Treatment of I with 1 eq. of trimethyl phosphite in benzene at room temperature for 16 hr followed by purification by silica gel column chromatography gave the 7α,7α'-dimer of Schiff base [II; froth, 62%; δ^{CDCl_3} 5.55 (C-6 H), 8.66 (CH=N)], 7α-dimethylphosphono Schiff base [IIIa; froth, 30%; δ^{CDCl_3} 3.59 and 3.70 (d, J=11, P-OCH_3), 5.26 (d, J=8, C-6 H), 8.69 (d, J=5, CH=N)] and 7β-dimethylphosphono Schiff base [IIIb; froth, 4%; δ^{CDCl_3} 3.80 (d, J=11, P-OCH_3), 4.93 (d, J=6, C-6 H), 8.65 (d, J=4, CH=N)]. Hydrolysis of II with a small amount of 3N hydrochloric acid in acetone at room temperature for 1 hr gave the imidazolidine [V; froth, 57%; δ^{CDCl_3} 1.39 ($(CH_3)_2C$), 4.89 (C-6 H)], while treatment of II with 2,4-dinitrophenylhydrazine and p-toluenesulfonic acid in ethanol afforded 7α,7α'-dimer of amino compound [IV; froth, 64%; δ^{CDCl_3} 5.01 (C-6 H)]. Acetylation of IV with phenylacetyl chloride and N,N-diethylaniline followed by removal of diphenylmethyl group with trifluoroacetic acid gave 7α,7α'-dimer of 7-phenylacetamidocephalosporanic acid [VII; powder, 64%;

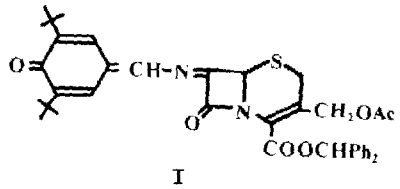
ν_{max}^{nujol} 3250, 1735, 1680(sh) cm^{-1}; δ^{DMSO-d_6} 1.94 (OAc), 3.35 (C-2 H), 3.50 ($C_6H_5CH_2$), 4.56 and 4.86 (ABq, J=13, C-3 methylene), 5.25 (C-6 H), 7.12 ($C_6H_5CH_2$), 9.08 (NH)].

Hydrolysis of IIIa with 3N hydrochloric acid in acetone gave 7β-amino compound [VIII; froth, 45%; δ^{CDCl_3} 3.63 and 3.68 (d, J=11, P-OCH_3), 4.96 (d, J=7, C-6 H)] which was then converted to 7α-dimethylphosphono-7β-phenylacetamidocephalosporanic acid [X; froth, 91%; ν_{max}^{nujol} 3280(br), 1795, 1740, 1690(sh) cm^{-1}; δ^{DMSO-d_6} 2.00 (OAc), 3.58 (C-2 H and $C_6H_5CH_2$), 3.65 and 3.72 (d, J=11, P-OCH_3), 4.65 and 4.99 (ABq, J=13.5, C-3 methylene), 5.25 (d, J=6, C-6 H), 7.24 ($C_6H_5CH_2$), 9.08 (d, J=7, NH)], similar to the synthesis of VII.

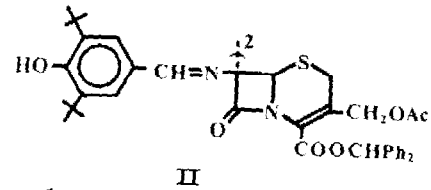
Compounds, II, IV, V, VI and VII, were assigned to dimers by the formation of the imidazolidine (V) from II and the mass spectrum of V which showed the relatively strong ion peak (m/e 152) corresponding to XI. Configuration at C-7 of these dimeric compounds was considered as bis-7α,7α'-configuration from the NMR spectra wherein each proton located at the corresponding position in each of the respective rings in these compounds showed the same chemical shift and the presumed mechanism for the formation of II. The quinoid (I) affected directly by trimethyl phosphite might react as a nucleophile with another quinoid (I) and the bond forming the dimer at C-7 might occur from the less hindered α side as shown below.



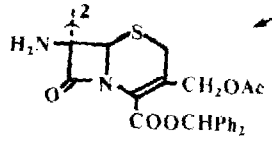
The structures of 7α-dimethylphosphono derivatives (IIIa, IIIb, VIII, IX and X) were confirmed by reasonable values for the coupling constants of $J_{p,C-6H}$=6 - 8 and $J_{p,CH=N}$=4 - 5 between the phosphine and C-6 H in these compounds as a three bond coupling and between the phosphine and imino proton in IIIa and IIIb as a four bond coupling (H-C=N-C-P), respectively. This assignment was supported by the mass spectrum of the methyl ester of X, prepared



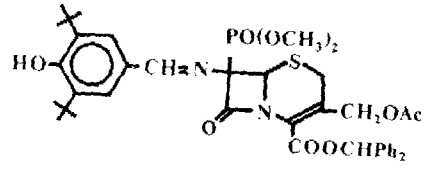
I



II

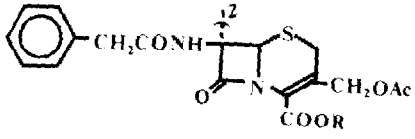


IV



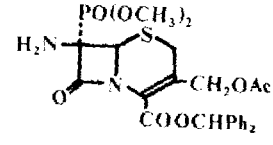
IIIa : 7α – $PO(OCH_3)_2$

IIIb : 7β – $PO(OCH_3)_2$

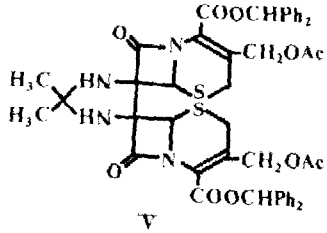


VI : R = $CHPh_2$

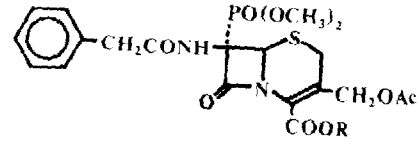
VII : R = H



VIII

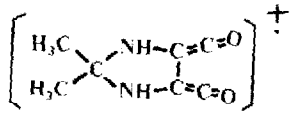


V

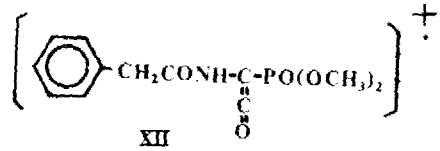


IX : R = $CHPh_2$

X : R = H



XI



XII

from X and diazomethane, which showed a molecular ion peak (m/e 512) and the ion peak of the fragment (XII). In the configuration at C-7 of III, it was assumed that the major product (IIIa) as compared to IIIb, would probably has the 7α-dimethylphosphono configuration because the nucleophilic attack of trimethyl phosphite on I would occur from the α side by reason of the steric hindrance mentioned above in the formation of II.

Compounds VII and X had no antibacterial activity.

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