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SYNTHESIS OF 7α-SUBSTITUTED CEPHALOSPORINS PART IV. NOVEL SYNTHESIS OF 7α-METHYLCEPHALOSPORINS

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In the search for useful 7-substituted cephalosporins, we have been investigating the reaction of a quinoid derivative (I) with various nucleophiles[1] At this time we would like to report the synthesis of 7-methylcephalosporins derived from I and a Grignard reagent. The previous known method[2] for preparation of 7-alkylcephalosporins employed electrophilic substitution of alkyl halides with C-7 cephalosporin carbanions. Our present work deals with the selective attack of a Grignard reagent, a strong nucleophile, on the quinoidal conjugated system in I, and not on the cephem nucleus.

Treatment of Ia with 1 eq. of methylmagnesium bromide in THF at -78° for 1 hr followed by dilution of the reaction products with ethyl acetate, washing with water and then purification by silica gel column chromatography (ethyl acetate - benzene) afforded the mixture of 7α- and 7β-methyl Schiff bases (IIa and IIb; 58%). The mixture of IIa and IIb was hydrolyzed with 3N hydrochloric acid in acetone to give the mixture of the amines, IIIa and IIIb, which were separated by silica gel column chromatography (ethyl acetate - benzene): IIIa [20.2% from I; δ^{CDCl_3} 1.54 (C-7 CH_3), 4.52 (C-6 H)] ; IIIb [4.6% from I; δ^{CDCl_3} 1.43 (C-7 CH_3), 4.54 (C-6 H)] . Acylation of IIIa and IIIb with phenylacetyl chloride gave IVa and IVb, respectively: IVa [95%; δ^{CDCl_3} 1.82 (C-7 CH_3), 4.77 (C-6 H)] ; IVb [83%; δ^{CDCl_3} 1.53 (C-7 CH_3), 5.06 (C-6 H)] . Removal of diphenylmethyl group of IVa with trifluoroacetic acid afforded 7α-methyl-7-phenylacetamido-3-deacetoxycephalosporanic acid[2c] [Va; 61%, mp 103~105°(d); ν_{max}^{nujol} 3300, 1775, 1720, 1700 cm^{-1}; δ^{DMSO-d_6} 1.63 (C-7 CH_3), 1.93 (C-3 CH_3), 3.29 (C-2 H),

3.49 ($C_6H_5CH_2$), 4.78 (C-6 H), 7.22 ($C_6H_5CH_2$), 8.62 (NH)].

Configuration at C-7 was confirmed by NOE values of IVa and IVb. The major product (IVa) gave 17 and 0% NOE values for C-6 H - C-7 CH_3 and C-6 H - C-7 NH interactions, respectively, while IVb gave 5 and 4% NOEs for the same interactions.

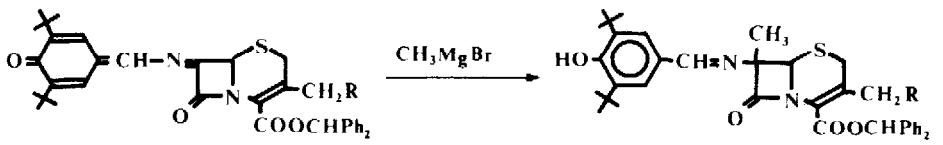
By this methylation sequence Vc [mp 145-146°(d), δ^{DMSO-d_6} 1.64 (C-7 CH_3), 4.82 (C-6 H)] and Vd [powder, δ^{DMSO-d_6} 1.66 (C-7 CH_3), 4.87 (C-6 H)] were successively produced.

Compounds Va, Vc and Vd showed MIC of 200, 25 and 12.5 g/ml against Staphylococcus aureus 209P, respectively.

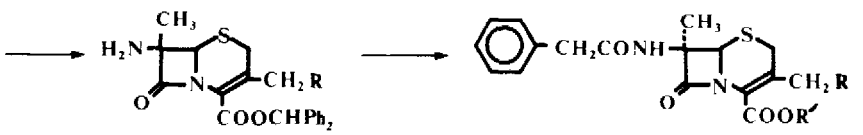
References

1) H. Yanagisawa, M. Fukushima, A. Ando and H. Nakao, Tetrahedron Lett., 2705 (1975); ibid., 259 (1976).

2) (a) E. H. W. Bohme, H. E. Applegate, B. Toeplitz, J. E. Dolfini and J. Z. Gougoutas, J. Amer. Chem. Soc., 93, 4324 (1971). (b) R. A. Firestone, N. Schelechow, D. B. R. Johnston and B. G. Christensen, Tetrahedron Lett., 375 (1972). (c) E. H. W. Bohme, H. E. Applegate, J. B. Ewing, P. T. Funke, M. S. Puar and J. E. Dolfini, J. Org. Chem., 33, 230 (1973).



I II

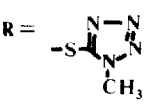


III

IV : R′ = $CHPh_2$

V : R′ = H

a : R = H ; 7α-CH_3 b : R = H ; 7β-CH_3

c : R = OAc ; 7α-CH_3 d : R =  ; 7α-CH_3