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TOTAL SYNTHESIS OF β-LACTAM ANTIBIOTICS I. α-THIOFORMAMIDO-DIETHYLPHOSPHONOACETATES

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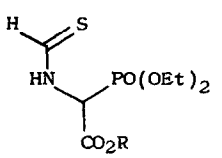
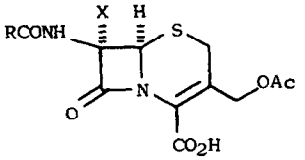
Since the structure elucidation of cephalosporin C in 1961,[1] the total synthesis of cephalosporins[2] has been the object of considerable interest. The preparation of a series of semi-synthetic 7α-methoxy substituted cephalosporins[3] possessing especially desirable antimicrobial properties has stimulated our efforts toward total synthesis. For commercial reasons, such a synthetic effort must be both unique and simple. The present series of papers describes a practical total synthesis of cephalosporins and 7α-methoxy substituted cephalosporins. This paper describes the synthesis of α-thioformamido-diethylphosphonoacetates (I), key intermediates for further elaboration to 6-H cephalosporins (II).[4]



I



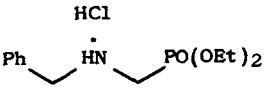
II

1,3,5-Tribenzylhexahydro-s-triazine[5] reacted with 3 equivalents of diethylphosphite at 100° for 6 hours to afford N-benzyl aminomethyldiethylphosphonate, conveniently isolated from Et_2O as its hydrochloride salt 1: 68%; mp 85-87°; nmr (D_2O) τ 8.58 (t, J = 7Hz, CH_3), 6.42 (d, J_{HP} = 14 Hz, CH_2P), 5.72 (d of q, J_{HP} = 8Hz and J = 7Hz, CH_2CH_3), 5.24 (s, CH_2Ph), and 2.43 (s, ArH). Hydrogenolytic debenzylation of 1 over 10% Pd-C in EtOH followed by neutralization with NH_3 in $CHCl_3$ gave aminomethyldiethylphosphonate (2) in near quantitative yield: ir (CCl_4) 8.06, 9.41, and 9.69μ; nmr ($CDCl_3$) τ 8.67 (t, J = 7Hz, CH_3), 7.03 (d, J_{HP} = 11 Hz, CH_2P), and 5.86 (p, J = 7Hz,

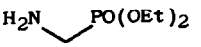
CH_2CH_3). The Schiff base 3 was prepared in 96-100% yield by stirring amine 2 with benzaldehyde at 0° followed by azeotropic removal of the water formed: ir (CCl_4) 6.09, 8.00, 9.42, and 9.64μ; nmr ($CDCl_3$) τ 5.93 (d of d, J_{HP} = 17.5 Hz and J = 1Hz, CH_2P) and 1.75 (t of d, J = 1Hz and J_{HP} = 5Hz, N=CH).

The Schiff base anion, prepared from 3 and one equivalent of PhLi in THF at -78°, was treated with methyl chloroformate and the reaction mixture was allowed slowly to warm to 0°. Chromatographic purification of the reaction mixture on silica gel gave recovered 3 and acylated Schiff base 4 in 37-43% yield: ir (CCl_4) 5.71, 6.10, 7.94, 9.46, and 9.72μ; nmr ($CDCl_3$) τ 6.22 (s, OCH_3), 5.25 (d, J_{HP} = 21 Hz, CHP) and 1.60 (d, J_{HP} = 5Hz, N=CH). The benzylidene group was removed by exchange with 2,4-DNPH·TsOH in EtOH, or better, with p-TsOH·H_2O in Et_2O. Neutralization of the resulting, gummy p-toluenesulfonate salt with K_2HPO_4 gave methyl α-amino-diethylphosphonoacetate (5a) in 73% yield: ir (CCl_4) 2.94, 5.72, 7.96, 9.48, and 9.70μ; nmr ($CDCl_3$) τ 8.17 (br s, NH_2), 6.20 (s, OCH_3), and 6.06 (d, J_{HP} = 20 Hz, CHP). By employing the same procedures, esters 5b-5e were prepared from the corresponding chloroformates.

Thioformylation of amino ester 5a with ethyl thionoformate[6] in CCl_4 proceeded smoothly, affording thioformamide 6a in 69% yield: ir (CCl_4) 3.13, 5.71, 7.01, 8.07, and 9.70μ; nmr ($CDCl_3$) τ 6.18 (s, OCH_3), 3.96 (d of d, J_{HP} = 22 Hz and J = 8.5 Hz, CHP), 0.50 (d, J = 6Hz, S=CH), and 0.27 (br m, NH); uv (EtOH) 265 (e 13,460)mμ. Benzyl ester 6b was obtained analogously. The remaining esters, 5c-5e, behaved differently when subjected to the above thioformylating conditions. For example, amino ester 5e gave amidine 7a, and 5c afforded mainly imidazole 8. Compound 8 presumably formed by intramolecular elimination of CCl_3CH_2OH from amidine intermediate 7b. By thioformylating with excess EtOCSH in liquid H_2S at room temperature under autogenous pressure,[7] derivatives 6c, 6d, and 6e were obtained in 75, 89, and 70% yield, respectively: 6e has mp 92-94°; ir (CCl_4) 3.14, 5.72, 7.00, 8.01, and 9.65μ; nmr ($CDCl_3$) τ 6.20 (s, OCH_3) 4.81 (s, CH_2Ar), 3.96 (d of d, J_{HP} = 22 Hz and J = 8Hz, CHP), 3.11 (d,2, J = 9Hz, ArH), 2.66 (d,2, J = 9Hz, ArH), 0.73 (br m, NH), and 0.50 (d, J = 5Hz, S=CH); uv (EtOH) 223 (e 13,700) and 261 (e 14,600)mμ; m/e 375 (M^+).



1



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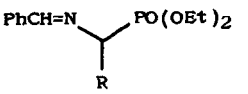
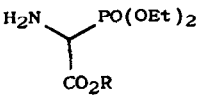
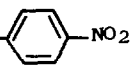
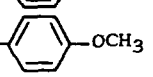
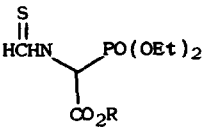
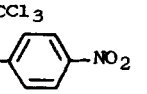
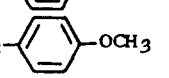


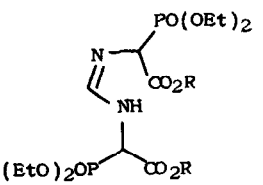
3, R = H
4, R = CO_2CH_3

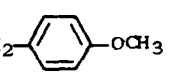


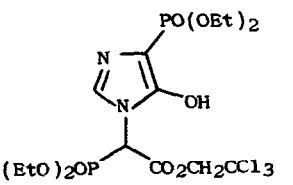
5a, R = CH_3
5b, R = CH_2Ph
5c, R = CH_2CCl_3
5d, R = 
5e, R = 



6a, R = CH_3
6b, R = CH_2Ph
6c, R = CH_2CCl_3
6d, R = 
6e, R = 



7a, R = 
7b, R = CH_2CCl_3



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