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THE SYNTHESIS OF S-METHYL AND O-METHYL β-LACTAM ANTIBIOTICS

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The current interest in synthesizing β-lactam antibiotics which are substituted in the position α to the β-lactam carbonyl has been prompted by two events First, Strominger and Tipper have suggested that 6-methyl penicillins and 7-methyl cephalosporins should have enhanced antimicrobial activity[1], and second, certain naturally occurring 7-methoxy cephalosporins have been found to possess unique antimicrobial properties[2,3] Considerable effort has been directed toward the alkylation and methoxylation of this position[4,5,6,7,8,9], and recently, two groups have successfully obtained 6-methyl penicillins and 7-methyl cephalosporins[10,11]. Using a similar procedure (activation by an appropriate Schiff base), we have also synthesized these methyl compounds as well as a number of other alkyl and acyl derivatives[12]. In addition, this procedure has led to the successful synthesis of S-alkyl and O-alkyl derivatives which we would like to report at this time.

The Schiff bases, Ia and IIa and b, were prepared in good yield by stirring the 6-APA, 7-ACA, and 7-ADCA trichloroethyl esters with p-nitrobenzaldehyde in absolute ethanol for 30 min at room temperature. In a typical synthesis of the S-methyl derivatives, 5 mmole of Ia dissolved in DMF was added to a 5 mmole solution of lithium diisopropyl amide at -78°, forming the deep blue anion. After 5 to 10 min, 10 mmoles of methoxycarbonylmethyl disulfide[13] in DMF was added and the reaction was gradually warmed to room temperature to give a quantitative yield of the S-methy Schiff base, Ib.

The conversion of the Schiff base to the free amine was effected in good yield by treatment with Girards "T" reagent in aqueous DMF The free amine was then acylated in the standard fashion to give the desired amide (IIIa,b) in about 25% overall yield following chromatography. For IIIa. nmr ($CDCl_3$) δ; 1.51 (s, 6, $-CH_3$), 2.28 (s, 3, $-SCH_3$), 4.57 (d, 2, $-CH_2$), 4 79 (d, 2, $-CH_2$), 5 67 (s, 1, C_5-H), 6.87-7 52 (m, 5, phenyl and NH), ir, mass spec, and elemental analysis gave proper values Support for the α addition of the S-methyl group is analogous with the alkylation reactions in which addition to the anion was found to occur exclusively at the α-face

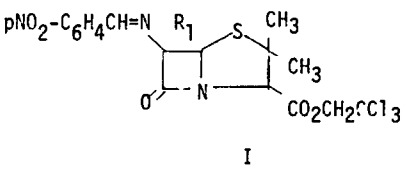
due to steric control[11].

In the same manner as described for IIa,b above, derivatives in the 7-ACA and 7-ADCA series were also prepared (IVa,b,c,d). Cleavage of the trichloroethyl esters to give the free acids was carried out in the usual manner with zinc and formic acid. Test results on a variety of different organisms showed these S-methyl compounds to have very low antimicrobial activity.

Despite their low activity, the S-methyl compounds were useful intermediates in the synthesis of the more interesting alkoxy derivatives[14] As a typical example, 1 mmole of IIIa in methylene chloride was cooled to -78°, and 1 mmole of chlorine in methylene chloride was added. After 5 min, 1 mmole of triethylamine in a solution of methanol was added. The desired methoxy compound, IIIc, was obtained in 65% yield following chromatography. For IIc nmr ($CDCl_3$) δ 1 55 (s, 6, $-CH_3$), 3 56 (s, 3, $-OCH_3$), 4.60 (s, 2, $-CH_2$), 4 82 (s, 2, $-CH_2$), 5.68 (s, 1, C_5-H), 6.82-7 66 (m, 5, phenyl and NH), ir, mass spec, and elemental analysis gave proper values.

The mechanism of the reaction apparently involves initial selective formation of the chlorosulfonium chloride V, which may be followed by elimination to give acylimine VI Baldwin has shown that such acylimines readily undergo nucleophilic attack by alcoholic solvents to give the alkoxy derivatives[15]. Only one C_6-methoxy isomer was obtained, and support for α-addition is found in the analogous alkylation reactions, which are sterically specific and yield only the α-substituted compounds[11] The α-configuration is further substantiated by the antimicrobial activity discussed below

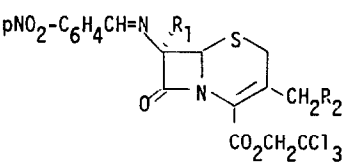
Cleavage of the trichloroethyl ester of IIIc to give the free acid was readily accomplished with zinc formic acid The methoxy derivatives (from IIIc, IVe,f) obtained in this manner were tested against a variety of organisms and were found to be much more active than either the corresponding methyl or S-methyl compounds. Using the same procedure, other alkoxy derivatives (from IIId,e) could also be prepared, but a rapid drop in activity occurred as the size of the alkoxy group increased Further investigations in this area are underway



I

a R_1=H

b R_1=CH_3S-



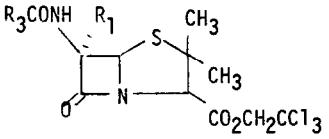
II

a· R_1=H, R_2=H

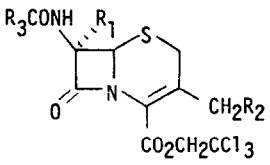
b R_1=H, R_2=AcO-

c R_1=CH_3S-, R_2=H

d R_1=CH_3S-, R_2=AcO-



III



IV

a R_1= CH_3S-, R_3= $PhOCH_2$-

b R_1= CH_3S-, R_3= $PhCH_2$-

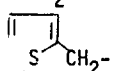
c R_1= CH_3O- R_3= $PhOCH_2$-

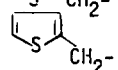
d R_1= CH_3CH_2O-, R_3= $PhOCH_2$-

e R_1= $(CH_3)_2CHO$-, R_3= $PhOCH_2$-

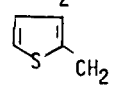
a R_1= CH_3S-, R_2= H, R_3= CH_3-

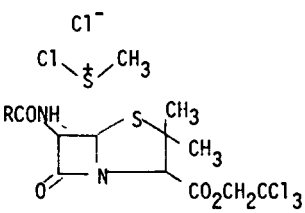
b R_1= CH_3S-, R_2= H; R_3= $PhOCH_2$-

c R_1= CH_3S-, R_2= H, R_3= 

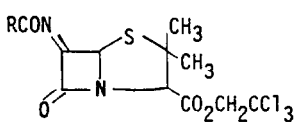
d R_1= CH_3S-, R_2= AcO-, R_3= 

e R_1= CH_3O-, R_2= H R_3= $PhOCH_2$-

f R_1= CH_3O-, R_2= AcO-, R_3= 



V



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