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α,β-DIHYDROXY-β-LACTAM DERIVATIVES [1]

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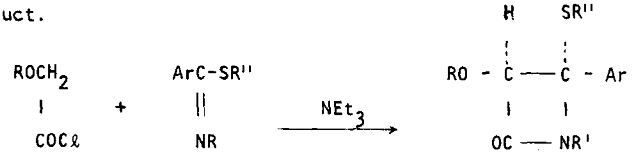
In view of the current interest in 7-alkoxycephalosporins and 6-alkoxypenicillins[2] we have been engaged in devising practical syntheses of alkoxy-β-lactams. We report here a convenient route to a series of 3,4-dihydroxy-2-azetidinone derivatives.

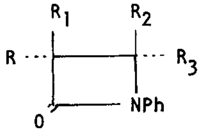
Previously we have shown that α-alkoxyacyl chlorides can be used for the annelation of imines to 3-alkoxy-2-azetidinones[3]. This method could not be extended to the synthesis of 3,4-dialkoxy-2-azetidinones since imido esters do not appear to undergo β-lactam formation. Thioimidates, however, have proved to be more reactive and various α-substituted-β-thioalkyl-β-lactams have been prepared in high yield by their reaction with appropriate acid chlorides and triethylamine.[4] The thioether group exerts a strong directive influence and a single isomeric form (E configuration) of the β-lactam is obtained thereby simplifying the isolation and purification of the product.



$$\begin{array}{c}ROCH_2\\ |\\ COCl\end{array} + \begin{array}{c}ArC\text{-}SR''\\ \|\\ NR\end{array} \xrightarrow{NEt_3} \begin{array}{ccccc} & H & & SR'' & \\ & \vdots & & \vdots & \\ RO - & C & — & C & - Ar\\ & | & & | & \\ & OC & — & NR' & \end{array}$$

Slusarchyk and coworkers[2b] have replaced SMe or OAc groups at C-7 of cephalosporins by reaction with mercuric acetate in methanol. Jen *et al.*[5] have interchanged the methylthio group with a methoxy group by the action of mercuric chloride and methanol on 6-methylthiopenams. We have now found that when E-1, 4-diphenyl-4-methythio-3-phenoxy-2-azetidinone (1) is refluxed with mercuric acetate in anhydrous methanol for about 15 min, the β-methoxy-β-lactam (2) is formed in good yield as a single isomer. The substitution occurred with retention as revealed by pmr spectroscopy[6]. Thus, both during the formation of the β-lactam and its transformation to (2) the steric hindrance between the SMe or OMe group and the OPh group appeared to

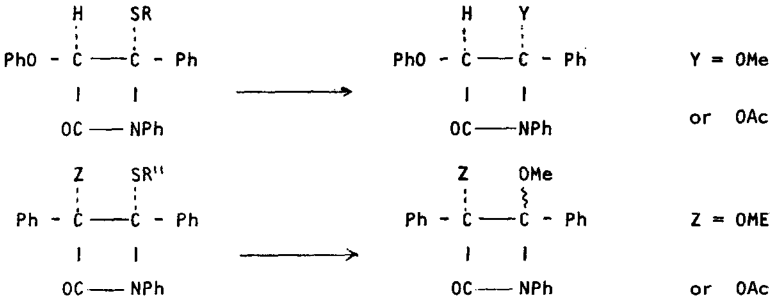
Substituted 3,4-Dihydroxy β-Lactams



	R	R1	R2	R3
1	OPh	H(4.40)	SMe(7.80)	Ph
2	OPh	H(4.30)	OMe(6.2)	Ph
3	Ph	OMe(6.42)	SMe(7.8)	Ph
4	Ph	OMe(6.20)	OMe(6.5)	Ph
5	Ph	OMe(6.90)	Ph	OMe(7.20)
6	Ph	OAc(7.80)	SMe(7.7)	Ph
7	Ph	OAc(8.10)	Ph	OMe(6.75)
8	Ph	OAc(8.35)	Ph	H(4.25)
9	Ph	H(4.95)	SMe(7.82)	Ph
10	Ph	H(4.50)	OAc(7.77)	Ph
11	OPh	H(4.48)	OAc(7.80)	Ph
12	Ph	OH	SMe(7.8)	Ph
13	Ph	OH	Ph	H(4.75)

* Values in parentheses refer to the chemical shift of the protons (τ units)

determine the steric course of the reaction. In contrast, the reaction of (3) with the same reagent led to two isomeric β-lactams (4) and (5) in nearly equal proportions. The high values of the chemical shift for both methyl groups in (5) indicate that each methyl group is near an aromatic ring; therefore C_3-OMe and C_4-OMe are assigned the *trans* configuration.



Attempts to replace the OAc group at C-3 with a methoxy group was unsuccessful even after prolonged refluxing of (6) with methanolic mercuric acetate; only the SMe group was interchanged for an OMe group resulting in the formation of (7) as a single isomer. The higher than usual values of the chemical shifts of OAc and OMe signals in 7 are indicative of their *cis* relationship to the aromatic rings and the E configuration for 7. The acetoxy group in 8 also was unresponsive to refluxing methanolic mercuric acetate.

A mild method for the replacement of the β-methylthio substituent was found to be 24 hr stirring at room temperature with mercuric acetate in ethylene glycol dimethyl ether. The β-lactams 1 and 9 gave single isomers 10 and 11, respectively. Both 3 and 6 produced mixtures of isomers. Thus, the steric course of replacement was the same with OAc as with OMe.

Through serendipity[7] a mild method of hydrolysis of the 3-acetoxy group in 6 and 8 was found to be 1 hr reflux with calcium chloride in aqueous methanol - the yield of α-hydroxy-β-lactams 12 and 13 was 70-80%. Since a hydroxy group can be transformed easily to acyloxy and alkyloxy groups, various mono and dialkoxy (or acyloxy) derivatives of β-lactams should be available through the methods discussed above.

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7. The breakage of a drying tube spilling partially hydrated $CaCl_2$ into a methanolic solution of a β-lactam was the beginning of an unplanned hydrolysis reaction.