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A CONVENIENT SYNTHESIS OF N-UNSUBSTITUTED beta-LACTAMS[1]

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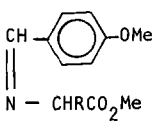
N-Unsubstituted β-lactams derived from penicillins[2] have been used recently for the elaboration of the bicyclic β-lactam systems of cephalosporins and analogs We have been interested therefore in converting easily synthesized monocyclic β-lactams to the corresponding N-unsubstituted derivatives For obtaining the appropriately substituted monocyclic β-lactams we have utilized the reaction of acid chlorides with imines in presence of triethylamine [3]

As a model compound, the β-lactam 3 was prepared by the reaction of phenoxyacetyl chloride and triethylamine on the Schiff base 1 from *p*-anisaldehyde and valine methyl ester hydrochloride A mixture of *cis* and *trans* β-lactams was formed but the *cis* compound could be isolated in 32% yield by fractional crystallization Normal saponification of the ester group was precluded by the sensitivity of the β-lactam ring to bases However, cleavage of the methyl ester group with lithium iodide in refluxing pyridine[4] provided the carboxylic acid 5 in 62% yield Decarboxylation of a carboxylic acid with lead tetracetate can lead to an olefin[5] or an acetate,[6] alternatively a halide can be formed[7] if lithium halide be present along with lead tetracetate When the β-lactam acid 5 in benzene solution was refluxed with lead tetracetate and a catalytic amount of cupric acetate[8] or an equivalent of lithium iodide, the acetate 6 was the only product isolated in 54% yield After some initial difficulty in the hydrolysis of the acetate 6, it was found that the hydroxy compound 7 could be obtained in 56% yield by stirring 6 with 30% trifluoroacetic acid for 15 min at room temperature

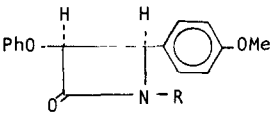
When 7 was subjected to Moffatt oxidation conditions[9] (dimethyl sulfoxide, N,N'-dicyclohexyl carbodiimide, pyridine, and trifluoroacetic acid) the product was unexpectedly found to be the N-unsubstituted β-lactam 8, mp 166-167° (yield 50%) The nmr spectrum of this compound displayed an ABX pattern (5 08, 5 61 and 8 83 δ, J_{AB} = 4 5Hz, J_{AX} = 2Hz and J_{BX} = ∿ 0Hz) consistent with the structure assigned A simpler method of converting the amidocarbinol 7

to 8 was found to be treatment with triethylamine in methylene chloride solution for a few hours at room temperature, the yield of the N-unsubstituted β-lactam (8) was 70% by this base-catalyzed cleavage of the aminal derivative (7)



1, R = i-Pr

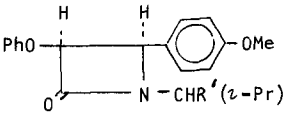
2, R = Me



3, R = -CH(i-Pr)CO_2Me

4, R = -CH(Me)CO_2Me

8, R = H



5, R′ = CO_2H

6, R′ = OAc

7, R′ = OH

In a similar set of experiments the Schiff base 2 from alanine methyl ester was converted to the *cis*-β-lactam 4, mp 133-135°, and then to 8 The method described here should be applicable to other monocyclic β-lactams with various α- and β-substituents and lead to N-unsubstituted β-lactams suitable as intermediates for the total synthesis of β-lactam antibiotics and analogs

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