

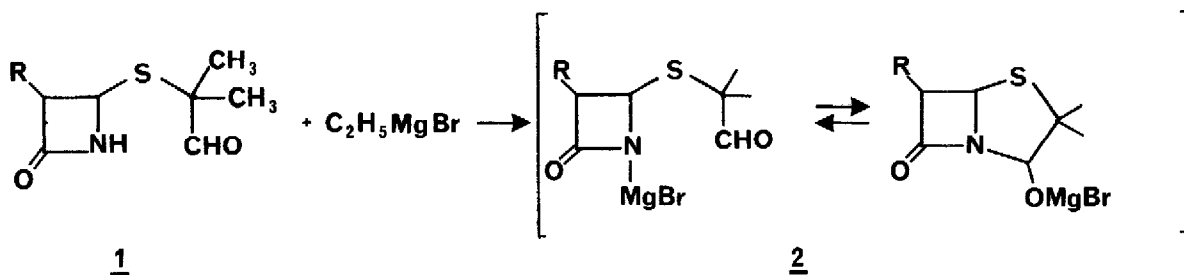
N-ACETYLATION AND N-HYDROXYMETHYLATION OF A PENICILLIN-DERIVED LACTAM SYSTEM UNDER MILD CONDITIONS

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N-Substitutions of β -lactam systems which are derived from or structurally similar to the penicillins, are not common reactions. Acetylations, hydroxymethylations, alkylations, and Mannich reactions have been reported¹ for special 3,3-disubstituted β -lactams. However, substitutions on the nitrogen atom of 2-azetidinones, which are mono-substituted at the 3-position and which contain a sulfur moiety on the 4-position are relatively rare^{2,3}. During the course of some recent work, we found that a penicillin-derived lactam system (1) could be N-substituted under novel and mild conditions. The method involved the apparent formation of an organomagnesium intermediate, 2, which was not isolated or identified, but was treated directly with acetyl chloride or formaldehyde. The aldehyde group of 1 was relatively inert toward ethylmagnesium bromide in

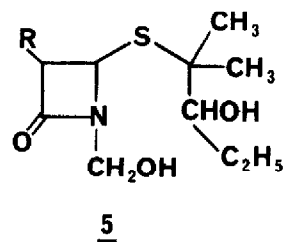
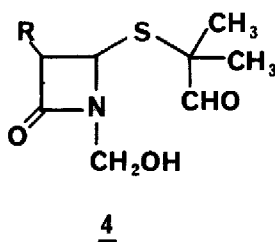
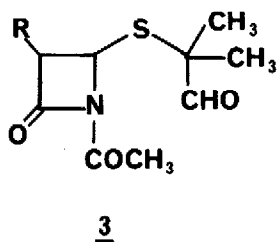


R = phthalimido

a normal Grignard reaction, probably because of the steric effect of the adjacent gem-dimethyl moiety and/or the equilibrium of the two forms of 2 in which the magnesium ion is bonded to the nitrogen and oxygen atoms. Direct acetylation of 1 was not tried, however alkylation using ethyl chloroacetate, 1, and triethylamine afforded only recovered starting material.

When compound 1^a (3.1 mmol) was treated with ethylmagnesium bromide (9.0 mmol) in tetrahydrofuran (30 ml) at room temperature, a gas was evolved which was assumed to be ethane. After 15 min, acetyl chloride (6.6 mmol) was added and the resultant mixture was stirred for about 1 hour. The latter was extracted between water and methylene chloride and the organic solvent-soluble fraction was chromatographed on silicic acid (80:20, ben-

zene:ethyl acetate). The second-fastest component easily crystallized from ether in 18% yield and was characterized as the N-acetylazetidinone, 3^S: ir (Nujol) 1805 (β -lactam carbonyl), 1785, 1725 (phthalimido), and 1720, 1710 cm^{-1} (aldehyde and imide).



In another experiment, the 2-azetidinone, 1 (2.5 mmol), THF (30 ml), and ethylmagnesium bromide (5.1 mmol) were stirred for 15 min. before formaldehyde (5.0 mmol) was added. After one hour, the mixture was hydrolysed with cold aqueous sulfuric acid. It was extracted with water and methylene chloride and the organic solvent-soluble fraction was chromatographed on silicic acid (50:50, benzene:ethyl acetate). The second-fastest zone crystallized from ether in 37% yield and was identified as the N-hydroxymethylazetidinone aldehyde, 4^S: mp 171-172°; ir (Nujol) 3520 (OH), 1790 (β -lactam carbonyl), 1780, 1720 cm^{-1} (phthalimido and aldehyde); nmr (CDCl_3) 1.28, 1.40 (s, 6, *gem*-dimethyls), 4.80 (q, 2, $-\text{CH}_2\text{OH}$), 5.02, 5.68 (d, 2, β -lactam hydrogens, $J=5\text{cps}$), 7.85 (m, 4, aromatic), and 10.00 δ (s, 1, aldehyde hydrogen). The third-fastest zone from the column crystallized from benzene in 19% yield and was characterized as the N-hydroxymethylazetidinone alcohol, 5^S: mp 185.5-186.5°; ir (Nujol) 3280, 3380 (OH), 1790 (β -lactam carbonyl), 1780, 1710 cm^{-1} (phthalimido); nmr (acetone- D_6) 1.0-1.6 (m, 11, *gem*-dimethyl and ethyl), 2.8 (s, 1, $>\text{CHOH}$), 4.2-5.2 (m, 4, β -lactam hydrogens and $-\text{CH}_2\text{OH}$), 7.6 δ (m, 4, aromatic hydrogens).

The novel penicillin derivatives, 3, 4, and 5, may be important intermediates in the synthesis of new bicyclic β -lactam compounds.

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- (3) R. B. Woodward, *et al.*, *Helv. Chim. Acta*, 55, 408 (1972).
- (4) 4-(1'-Formyl-1'-methylthio)-3-phthalimido-2-azetidinone (1) was prepared by the method of J. C. Sheehan and K. G. Brandt, *J. Am. Chem. Soc.*, 87, 5468 (1965), except that a benzene-free sample was crystallized from ether; mp 134-136°.
- (5) All new compounds gave satisfactory elemental analyses (within $\pm 0.3\%$).