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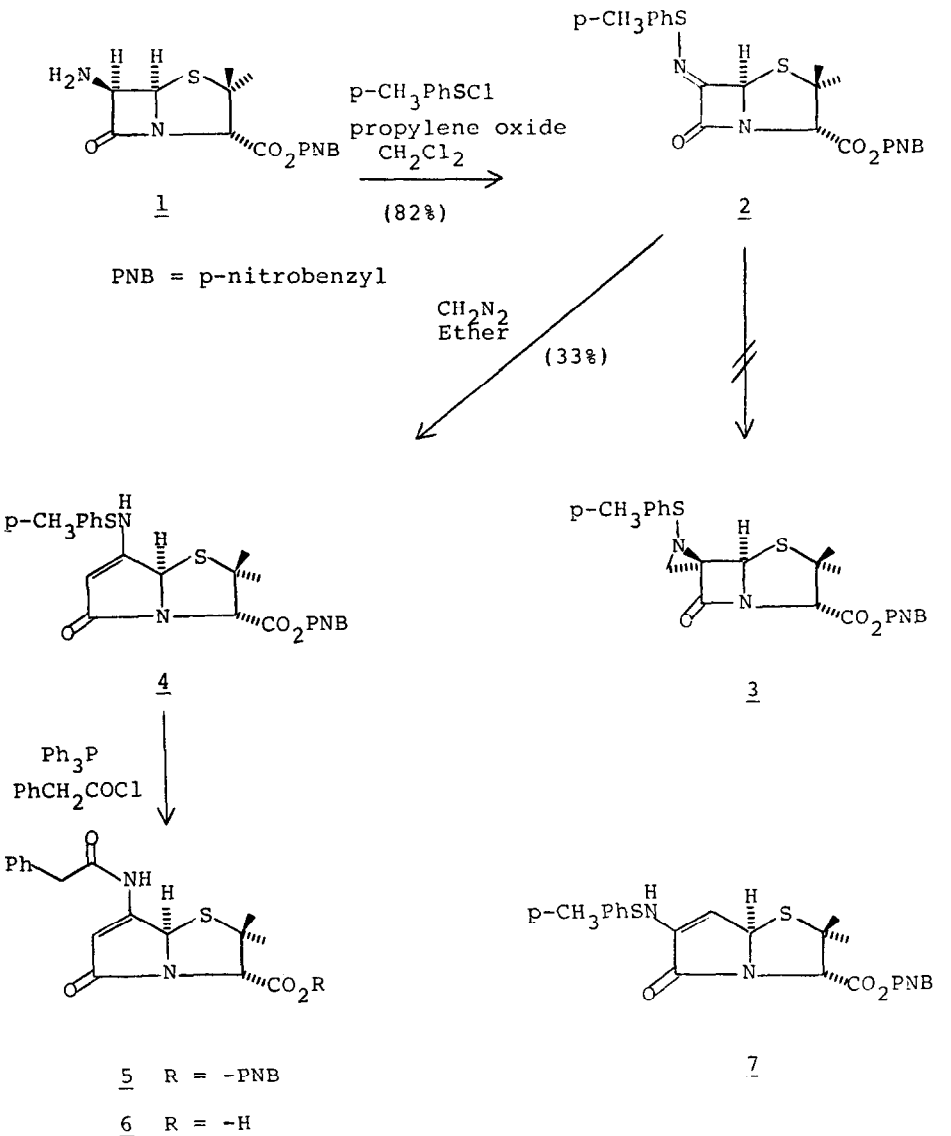
β-LACTAM RING REARRANGEMENT OF A 6-SULFENIMINOPENICILLANIC ACID

E. M. Gordon* and Jelka Pluščec
The Squibb Institute for Medical Research
Princeton, New Jersey 08540

Summary: Reaction of a 6-sulfeniminopenicillanic acid ester with diazomethane induces a β-lactam ring expansion rearrangement which proceeds via methylene insertion into the C(6)-C(7) bond.

In the course of investigations aimed at design of new β-lactam antibiotics and β-lactamase inhibitors we explored the chemistry of bicyclic sulfenimino β-lactams[1] and observed an unusual rearrangement of a 6-sulfeniminopenicillanic acid derivative. Earlier studies with α-amino acid derived sulfenimines[2] had shown that some of these substances reacted with diazomethane to yield N-sulfenyl aziridines.[3] The presently described work was predicated on extending these observations to sulfenimino β-lactams, with the intent of preparing spiro-aziridine 3.

Sulfenimine 2 was smoothly prepared (82%) from 6-aminopenicillanic acid p-nitrobenzyl ester (1) by treatment with p-toluenesulfenyl chloride in the presence of an acid scavenger (propylene oxide), according to a previously reported procedure.[1] These studies had also shown by x-ray crystallographic analysis that sulfenimino sulfur was disposed anti to the α-azetidinone carbonyl group. Reaction of 2 with diazomethane (ether, -5°C, 3 days) afforded a 33% yield of a new, colorless (2 is bright yellow), more polar product, as a white foam [IR ($CHCl_3$) 3400 br, 1745, 1685, 1605 cm^{-1}; m/e 485 (M^+); ^{13}C NMR (acetone-d_6) δ 20.4 (-CH_3), 32.9 (Ph-$\underline{CH}_3$), 60.7 (C-2), 65.6 (-$\underline{CH}_2PhNO_2$), 67.7,68.4 (C-3, C-5), 92.9 (O=$\underline{C}$-$\underline{CH}$=$\underline{C}$-NH-), 169.0 (O=$\underline{C}$-CH=$\underline{C}$-NH-), 171.1, 175.5 (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.43 (s, 3H), 2.28 (s, 3H), 4.73 (s, 1H), 5.18 (s, 1H), 5.23 (s, 2H), 5.73 (s, 1H), 6.35 (br s., 1H, ex.)] which, on the basis of this data, was assigned as sulfenamide 4. A key point in this assignment rests on the unusual ^{13}C NMR chemical shifts due to the olefinic carbons, which permits discrimination between isomeric structures 4 and 7. In the product these appear at 92.9 and 169.0 δ suggesting a highly polarized double bond. Olefinic carbon resonances of the model compound 3-amino-2-cyclohexenone (8) are observed at 97.6 and 168.4 δ in good agreement with assigned structure



1

2

3

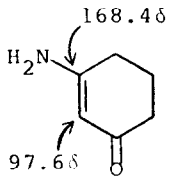
4

5 R = -PNB

6 R = -H

7

4. The olefinic carbon resonances of model 9 occur at 109.9(ß) and 138.2(α)δ hence, discounting 7 as a viable possibility.[4,5]



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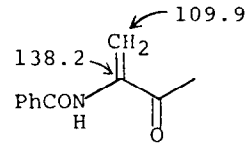

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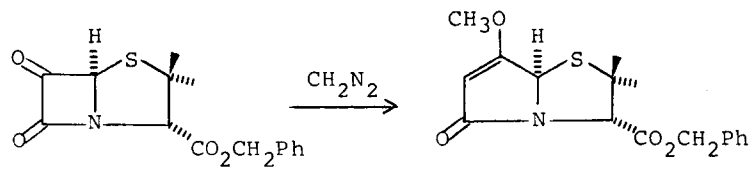
The aforementioned rearrangement apparently proceeds by methylene insertion into the C(6)-C(7) azetidinone bond. Precedent exists for similar insertion reactions of α-diketones.[6] More pertinent, however, to the present case is recently published work of Baldwin, *et al.*[7], wherein the transformation of benzyl 6-oxopenicillanate 10 to 11 with diazomethane is reported. More complex examples of C(6)-C(7) bond cleavage in other penicillin based rearrangements were recently reported by Jaxa-Chamiec[8] and Bycroft[9].



10 11

Substance 4 could not be acylated directly with phenylacetyl chloride (pyridine/CH_2Cl_2); however, prior sulfenamide cleavage initiated by triphenylphosphine followed by acylation and chromatography, directly afforded 5 [42%, ^1H NMR ($CDCl_3$) δ 1.40 (s, 6H), 3.68 (s, 2H), 4.66 (s, 1H), 5.30 (s, 2H), 5.66 (s, 1H), 6.16 (s, 1H), 9.05 (Br.s, 1H, ex.); IR ($CHCl_3$) 1740, 1700 br., 1620 cm^{-1}; UV (MeOH) 270 nm (ε = 18,700)]. Deprotection of 5 by the method of Lammert, *et al.*[10], using $Na_2S \cdot 9H_2O$/THF/0°-5°C/3h produced free acid 6 [83%, ^1H NMR (CD_3OD) δ 1.43 (s, 3H), 1.53 (s, 3H), 3.66 (s, 2H), 4.63 (s, 1H), 5.83 (s, 1H), 6.11 (s, 1H), 7.26 (s, 5H); IR ($CHCl_3$) 1700 br, 1620 cm^{-1}] which did not manifest significant antimicrobial or ß-lactamase inhibitory activity.

Until recently C(6)-C(7) rearrangement of the ß-lactam nucleus was unknown. The present example thus joins three other reports of the past year[7,8,9] in establishing under appropriate conditions the generality of such reactions.

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References

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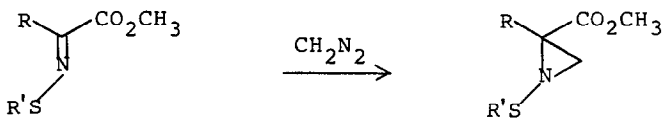

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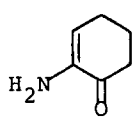
4. A more ideal model would be 2-amino-2-cyclohexenene (iii), however, this substance is not well known, presumably because of instability.



iii

α-Amino-α,β-unsaturated carbonyl compounds such as 7, 9, and iii possess rather unpolarized 1,4 systems, due to the influence and position of amino nitrogen, Such materials are thus expected to exhibit olefinic carbon resonances in the normally encountered range.

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