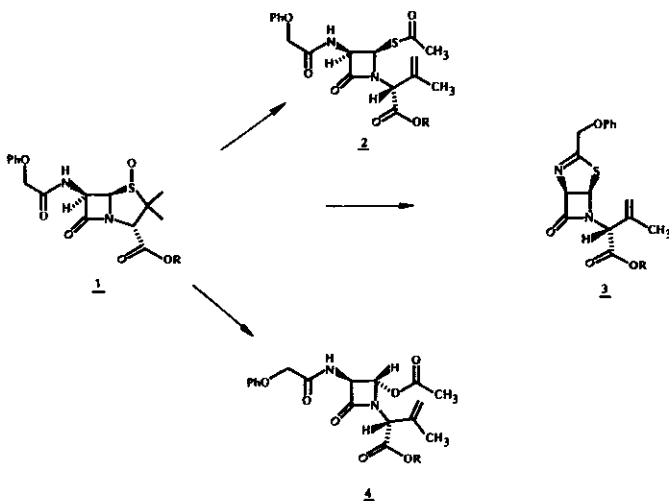


SUBSTITUENT EFFECTS ON THE COURSE OF THE REDUCTIVE ACYLATION OF PENICILLIN SULFOXIDE DERIVED SULFENATES

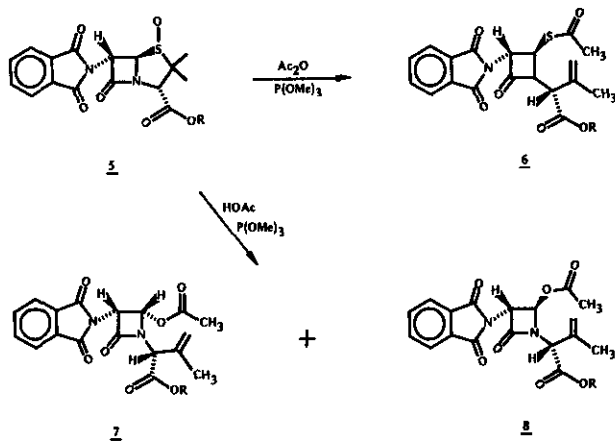
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Abstract: Reductive acylation of penicillanate sulfoxide derived sulfenates with trivalent phosphorous compounds and acetic anhydride has been shown to give β -lactam products resulting from either oxygen or sulfur transfer to phosphorous dependent on the substituent at the C-6 position of the penicillanate.

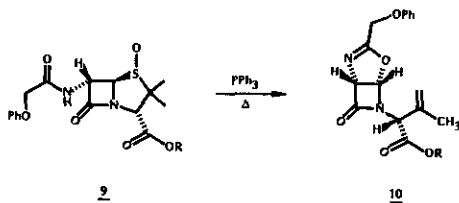
One of the many remarkable ramifications of the penicillin sulfoxide rearrangement¹ has been the versatile and intriguing Hatfield reductive acylation². Treatment of an ester of penicillin V sulfoxide **1** with acetic anhydride and trimethylphosphite in benzene at reflux produced in good yield the seco thio-acetyl β -lactam **2**. In the absence of acylating agent, thiazoline **3** had previously been isolated¹.



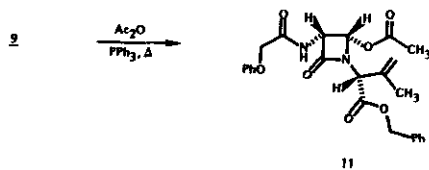
Recently, Lombardi and his coworkers have reported yet another course for the rearrangement³. In the presence of carboxylic acids the seco-O-acetyl β -lactam **4** is formed with inversion of configuration at C-5 (penicillin numbering). Replacement of the phenoxy acetamido side chain with phthalimido does not alter the course of the reductive acylation in the presence of either acetic anhydride¹ or acetic acid³. Reductive acylation of 6-epiphthalimido penicillanate sulfoxide **5**, also proceeds to thioacetyl product **6** with acetic anhydride⁴, but the O-acetyl derivatives obtained by treatment with trimethylphosphite and acetic acid have been found to have both *cis* and *trans* configurations (**7** and **8** respectively) at C-5 and C-6³. Yet another course for rearrangements of



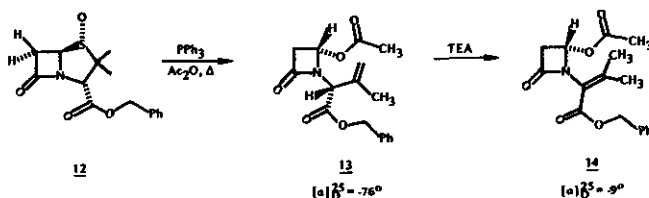
this type has been reported for 6-epipenicillanate sulfoxides represented by 9, which, in the absence of acylating agent or acid, produce oxazolines 10, useful intermediates in the synthesis of 1-oxa-cephems⁵.



In the course of our studies on the chemistry of β -lactam antibiotics we have encountered further intriguing anomalies in the reductive acylation of penicillanate sulfoxides. When 9 ($R = \text{CH}_3$) was refluxed in benzene with triphenylphosphine and excess acetic anhydride, conditions which convert 1 to 2 in good yield, none of the expected thioacetyl derivative, 6-epi 2, was obtained. In fact the same major product was observed whether the reaction was run in the presence of acetic acid or acetic anhydride.

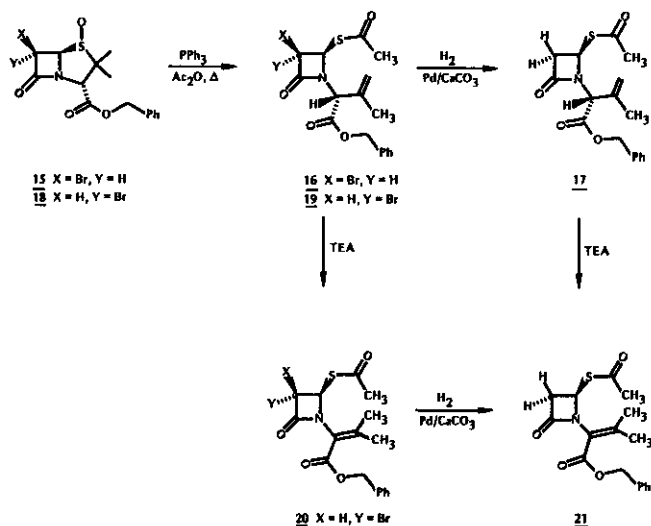


This major β -lactam product (30-60%) had the unexpected structure **11**, the *cis*-substituted β -lactam protons prominent in the proton nmr spectrum ($J = 3.5\text{Hz}$). The presence of the *trans* isomer of **11** ($J = 1.5\text{Hz}$) in the acetic acid procedure (*cis/trans* $\sqrt{3}/1$) was the principal distinction between product mixtures under the differing reaction conditions. Only the *cis* isomer **11** was found as an acetylated β -lactam product in the acetic anhydride reaction. Analysis by ^{13}CMR and high resolution mass spectroscopy confirmed the absence of sulfur in the molecule. Furthermore, triphenylphosphine sulfide was isolated in 64% yield, indicating transfer of sulfur to phosphorous. Thus neither the thioacylation nor predominant acetate displacement from the less hindered face was observed with substrate **9**. Similarly, penicillanate sulfoxide **12** gave under conditions of reflux in benzene with one equivalent of triphenylphosphine and five equivalents of acetic anhydride, an acetoxy azetidinone **13** (25-75%) which maintained optical activity on isomerization to α,β -unsaturated ester **14**. Triphenylphosphine sulfide was again isolated. Stereochemical preference for acetate substitution even in the absence of a C-6 substituent was apparent⁶.



Again, the same product **13** was observed whether acetic acid or acetic anhydride was used, and this material was found to possess the (*S*) stereochemistry at the former C-5 position (penicillin numbering), the result of an inversion of configuration at that center (*vide infra*).

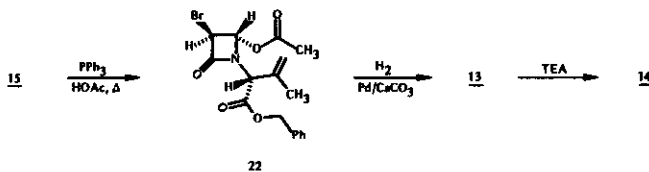
On the other hand, reductive acylation of benzyl 6- β -bromopenicillanate⁷ sulfoxide **15** under identical conditions in the presence of excess acetic anhydride gave **16** (50%), which retained a *cis*-substituted β -lactam ($J = 4\text{Hz}$) and the sulfur atom (^{13}CMR , 192 ppm). Reduction of the bromo



β -lactam 16 gave 17, the product which might have been expected to result from reductive acylation of 12. As a control experiment 17 was subjected to the same reaction conditions (triphenylphosphine and either acetic acid or acetic anhydride in refluxing benzene) and was found stable, no 13 being formed, eliminating the remote possibility that 17 was a transient intermediate in the conversion of 12 to 13.

Benzyl 6- α -bromopenicillanate⁶ sulfoxide 18 also produced a thioacetyl product 19 (60%) under identical reductive acylation conditions, with triphenylphosphine or triethylphosphite. Isomerization of 19 with triethylamine gave crystalline (mp 79-80°) 20 in quantitative yield. Cleavage of the carbon-bromine bond by hydrogenolysis gave optically active β -lactam 21 ($(\alpha)_{\text{D}}^{25}(\text{CHCl}_3) + 106^\circ$).⁶

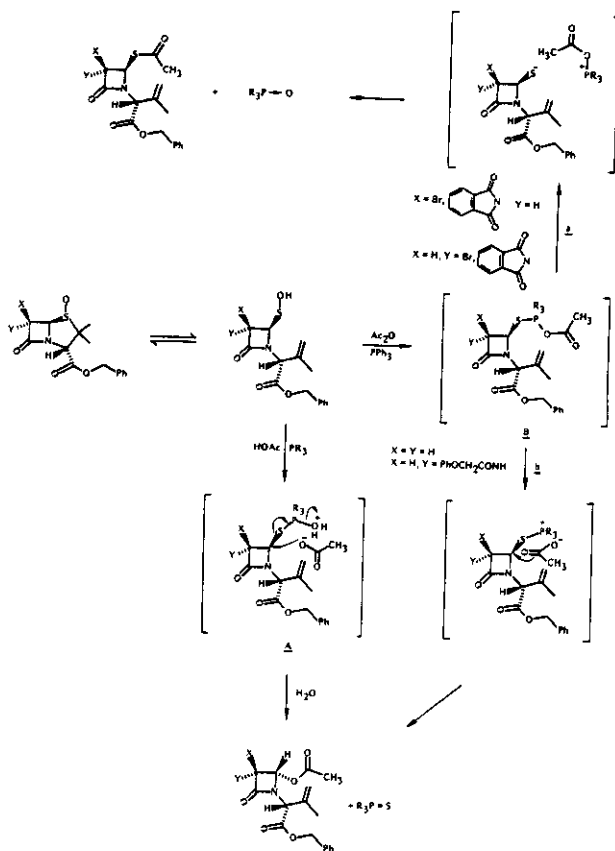
In the presence of excess acetic acid, the 6- α -bromo epimer 18 gave a plethora of products, in poor yield. The 6- β -bromo sulfoxide 15 gave trans substituted ($J = 1.5\text{Hz}$) β -lactam 22 in 13% yield, among several other products. No cis β -lactam products were detected.



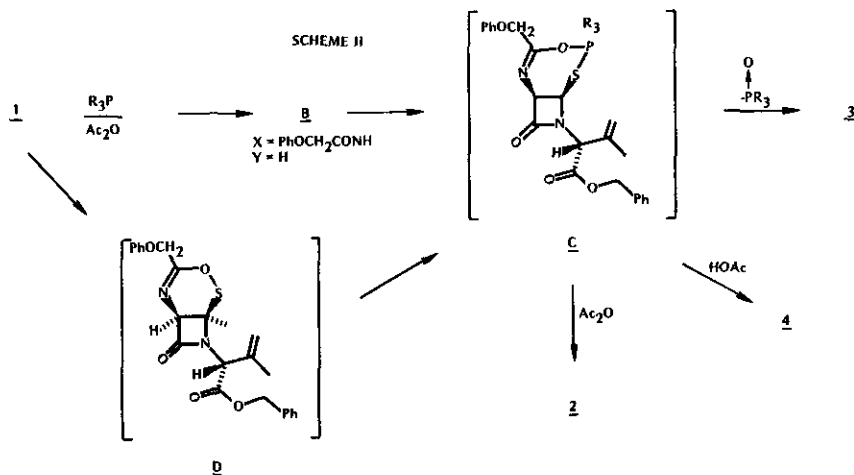
The bromine atom in 22 serves as a stereolabel, allowing assignment of the (S) configuration to the former C-5. Conversion of 22 to 13 proceeded under hydrogenolysis conditions and gave material identical in every way to 13 formed from 12. Isomerization with triethylamine gave 14 with a single asymmetric center and of the same optical rotation ($(\alpha)_D^{25}$ (CHCl₃) - 9°) as the sample originally derived from 12. Thus the reaction of 12 with triphenylphosphine and either acetic anhydride or acetic acid provided inversion of configuration on substitution by acetate at the former C-5 position.

These experiments suggest that the C-6 substituent of a penicillanate sulfoxide plays a pivotal role in the determination of product structure under Hatfield conditions. Mechanistically, we feel these data are best accommodated by the formulation of Scheme I.

SCHEME I



Under acid conditions the penta-coordinate phosphorous intermediate A⁹ might lose water as a neutral fragment allowing Sn2 displacement by carboxylate with phosphine sulfide as leaving group. In the event that the incoming nucleophile or the C-6 substituent is sterically encumbering, an Sn1 component may attain increased importance resulting in partial or complete randomization of stereochemistry at C-5³. While no thioacetyl products have been reported under acid conditions, it would appear possible to observe them, should competing ligand exchange at phosphorous occur, resulting in penta-coordinate intermediate B. Species B may be formed directly in the presence of acetic anhydride and might account for both the thioacetyl (path a) and O-acetyl (path b) products. From our data, it seemed that fragmentation of the intermediate B was controlled by the substituent at C-6, the more electron withdrawing substituents (bromo, phthalimido) following path a to thioacetyl products, regardless of C-6 stereochemistry. The weaker electron withdrawing moieties (phenoxyacetamido, hydrogen) allowed fragmentation by way of path b producing O-acetyl products with inversion of configuration¹⁰. The paradox, of course, is that reductive acylation of 1, the progenitor of these studies, gave a thioacetyl product, differing from the inverted O-acetyl product of its C-6 epimer 9. We believe this anomalous stereoregulation of reaction course may be explained within the framework of Scheme I through an alternate mode possible with cis-amido sidechain (Scheme II).



Side chain participation in the penicillin sulfoxide-sulfenate rearrangement has ample precedent¹¹. Intermediate C may result from internal phosphorous ligand exchange in B, or from direct reduction of a hypothetical but plausible cyclic sulfenate D¹¹. In the absence of acid, hypothetical penta-coordinate phosphorous intermediate C must fragment via phosphorous-sulfur bond cleavage. Subsequent acylation of sulfur and hydrolysis then proceed to give observed product 2. In the absence of acylating agent, phosphine oxide could be eliminated providing the driving force for cyclization

to 3. Finally, in the presence of acid, protonation of the C-6 nitrogen could impel phosphorous-oxygen bond dissociation with subsequent substitution at C-5, primarily with inversion.

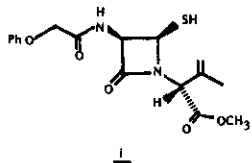
In summary, the Hatfield reductive acylation pursues a course dictated in large measure by the substituent present at C-6 of the penicillanate sulfoxide nucleus. The results seem most generally rationalized in terms of penta-coordinate phosphorous intermediates (A, B and C) and their fragmentation which appears to be controlled in part by the electron withdrawing capabilities of the substituents and their capacity for intramolecular participation in the reaction.

Acknowledgment. The authors thank Dr. Gwen Chmurny and Mr. Richard Ware for spectral studies.

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