Table I. Quantum Yields for C–S Cleavage[a] of RSSR

R	Sensitizer	ϕ_{RH}[b]
t-C_4H_9	Ph_2CO	0.34
$PhCH_2$	$PhCOCH_3$	0.26 ± 0.003 (3 DF)
	Ph_2CO	0.21 ± 0.003 (10 DF)
	2-MAQ	0.17 ± 0.005 (5 DF)
c-C_6H_{11}	Ph_2CO	~0.007
n-C_6H_{13}	Ph_2CO	~0.001

[a] In purified, deoxygenated benzene 0.1 M in the corresponding mercaptan as a radical scavenger. Limiting quantum yields are reported.[14] Photolysis conditions were carefully adjusted so that <2% of the incident light is absorbed by the disulfides; [RSSR] ~ 0.4 M. Several actinometers were used; results for different actinometers are in good agreement. All hydrocarbon yields were determined gas chromatographically. Neither gas chromatographic nor uv analyses give any indication of important reactions other than C–S cleavage in any of these photolyses; uv analyses demonstrate that none of the sensitizers is consumed. Solvents and reactants were carefully purified by appropriate methods; purity was, in general, monitored by gas chromatography. [b] Precision stated as standard deviation of the mean; DF = degrees of freedom.

The use of mercaptan as a radical scavenger was applied to the photosensitized decomposition of several other disulfides. Quantum yields for C–S cleavage product, ϕ_{RH}, for a series of sensitizers and disulfides are reported in Table I.

It is clear that C–S cleavage is an important process in some cases and that the quantitative details are a function of both disulfide structure and sensitizer. The fate of the missing quanta is not known. A considerable body of qualitative evidence suggests that some are accounted for by S–S cleavage.[3,4] Unfortunately, there is no presently established method for quantitatively monitoring S–S cleavage in solution. An alternative possibility is that some "excited" disulfides return to ground state. Finally, cage recombination of the primary fragments can simply reverse the photochemical cleavage.[14] It is important to note that, in the absence of thiyl radical traps, S–S cleavage is apparently followed by the recombination of thiyl radicals to regenerate disulfide.[15] Thus, it is reported that direct photolysis (254 nm) of neat ethyl disulfide gives no apparent loss of disulfide, even though there is evidence for the formation of thiyl radicals.[15] Cyclohexyl and n-hexyl disulfides give comparable results; alkanes are formed in low yields by C–S cleavage, but the main characteristic of the photolyses is that there is no other apparent reaction. Thus, only alkanes are detected by gas chromatographic or ultraviolet analyses, sensitizer is not consumed, and (within the limits of the gas chromatographic analyses) neither mercaptans nor disulfides are consumed.[16]

In summary, these data qualitatively demonstrate the interaction of a variety of excited states with simple disulfides. C–S cleavage is clearly established as an important process in the photochemistry of *tert*-butyl and benzyl disulfides. Results for cyclohexyl and hexyl disulfides suggest that C–S cleavage may not be generally important when less stable alkyl fragments are formed. Nevertheless, these data provide the first quantitative details on the photosensitized decomposition of disulfides in solution. It will clearly be interesting to apply this method to the photodecomposition of cystine. Carbon–sulfur cleavage has been qualitatively identified in the direct photolysis of cystine.[17] Carbon–sulfur cleavage further provides an entry to the details of the interaction of sensitizers with disulfides; such a study will be reported in a separate paper.

Acknowledgment. This work was supported by a Public Health Service Grant, CA-06535, from the National Cancer Institute.

(15) K. Sayamol and A. R. Knight, *Can. J. Chem.*, **46**, 999 (1968).

(16) Since these analyses focus on the loss of starting materials at low conversion to hydrocarbon, the small amounts of disulfides consumed by C–S cleavage would not be detected. Any significant, unsuspected reaction which consumes disulfides would, however, have been observed.

(17) W. Forbes and W. Savige, *Photochem. Photobiol.*, **1**, 1 (1962).

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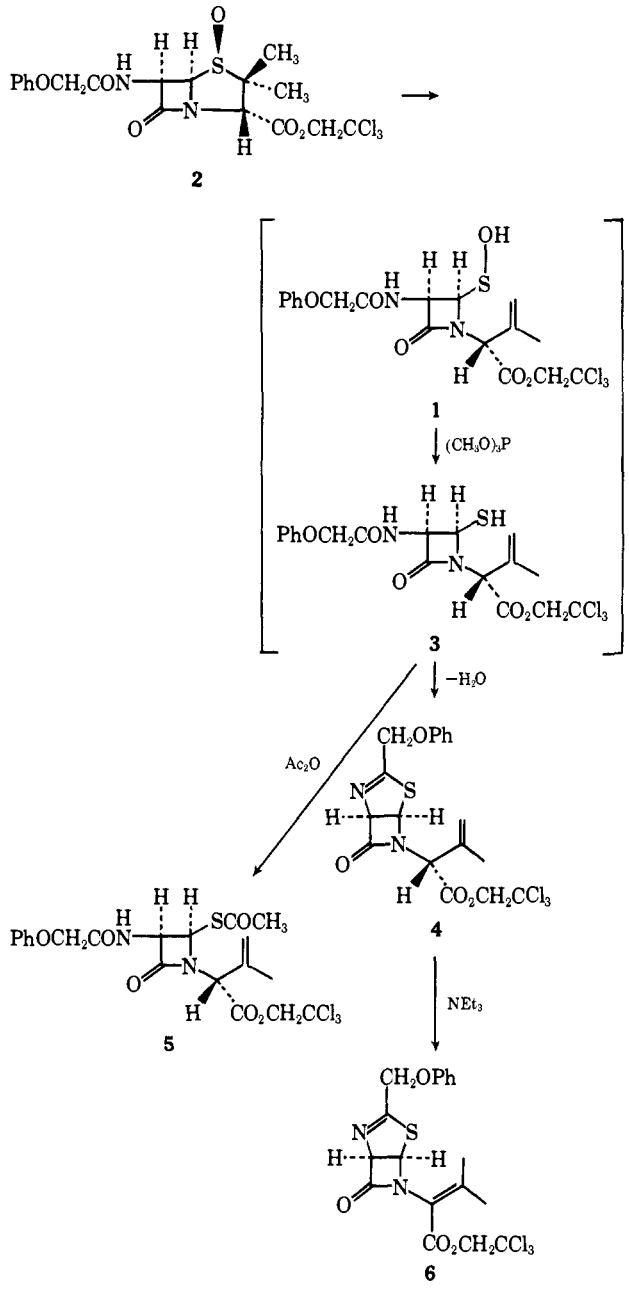
Structural Studies on Penicillin Derivatives. VIII. A Possible Model Biosynthetic Route to Penams and Cephems

Sir:

In previous publications[1-4] we described some of our investigations on the penicillin sulfoxide systems, in particular the mechanism of its rearrangement to a deacetoxycephem. In the original discovery of this rearrangement, Morin, *et al.*,[5] postulated that the reaction pathway proceeds through a sulfenic acid, a functionality of fleeting existence in aliphatic chemistry. Proof of its intermediacy was obtained by both ourselves[3] and other workers[6] using deuterium exchange techniques. We have also reported[4] that the penicillin sulfenic acid **1** is generated thermally from the sulfoxide **2** and can be trapped by reduction to thiol **3** using trimethyl phosphite. Subsequently, an intramolecular condensation product **4** of the intermediate thiol was isolated in high yield. Further interception of **3** was achieved[7] by acetic anhydride when the *S*-acetyl derivative **5** was isolated.

The thiazoline–azetidinone such as **4** is a derivative of L-cysteinyl-D-dehydrovaline and thus represents a model for a possible intermediate in the biosynthesis of penicillin and cephalosporin antibiotics (see Scheme I). In such a speculative biosynthetic pathway, the cysteine moiety may be protected either as a derivative of α-aminoadipic acid[8] or by attachment to a protein surface. The proposed course of events subsequent to protection of the cysteine moiety would be amidation with L-valine, followed by β-lactam ring closure (see Scheme I). The resulting derivative **7** is

(1) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).
(2) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).
(3) R. D. G. Cooper, *ibid.*, **92**, 5010 (1970).
(4) R. D. G. Cooper and F. L. José, *ibid.*, **92**, 2575 (1970).
(5) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **85**, 1896 (1963); (b) *ibid.*, **91**, 1401 (1969).
(6) D. H. R. Barton, F. Comer, D. C. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Commun.*, 1059 (1970).
(7) L. D. Hatfield, J. W. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Lett.*, 4897 (1970).
(8) This amino acid appears to play a key role in the biosynthesis of β-lactam antibiotics.[9]
(9) S. C. Warren, G. G. F. Newton, and E. P. Abraham, *Biochem. J.*, **103**, 891 (1967).



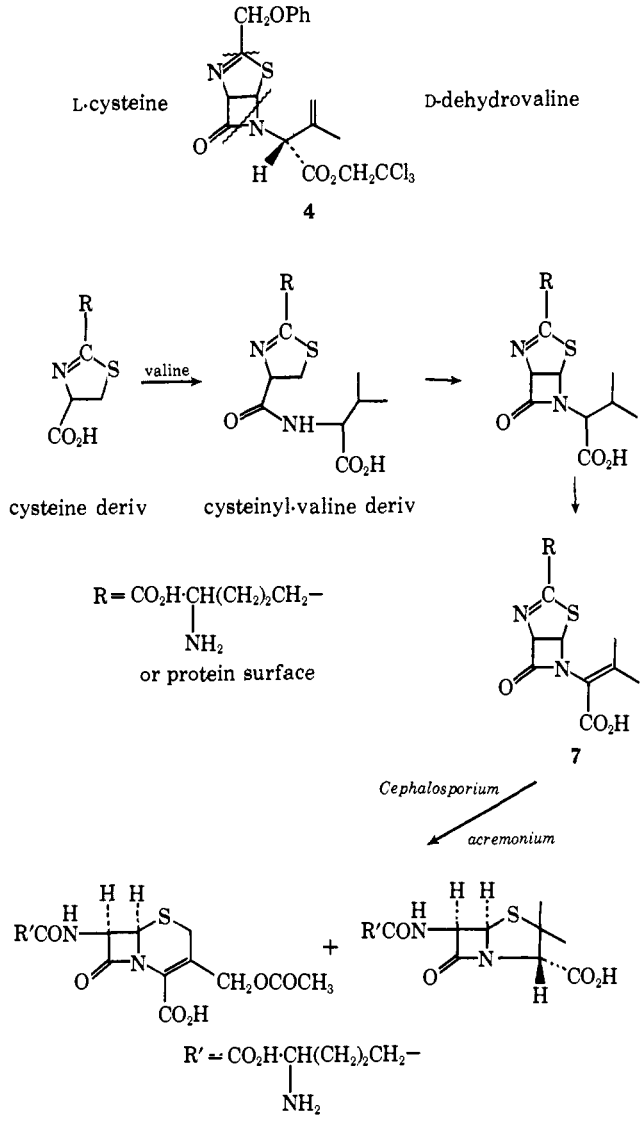
structurally similar to **6**, which is obtainable by base treatment of **4**.

The final step in a penam scheme, *via* the ring closure of the thiazolidine ring, is a Michael addition of a sulfur anion to α,β-unsaturated acid (**7**). This ring closure has already been demonstrated chemically by Wolfe and coworkers[10] who obtained the penicillin **8** from base hydrolysis of anhydropenicillin **9**. The correct stereochemistry at C-3 was obtained thereby giving the valine residue in penicillin the D configuration. Ring closure to a cephem would then involve an oxidative cyclization. Consequently, we investigated the oxidation of **4** under various conditions in an effort to chemically duplicate this biosynthetic postulate.

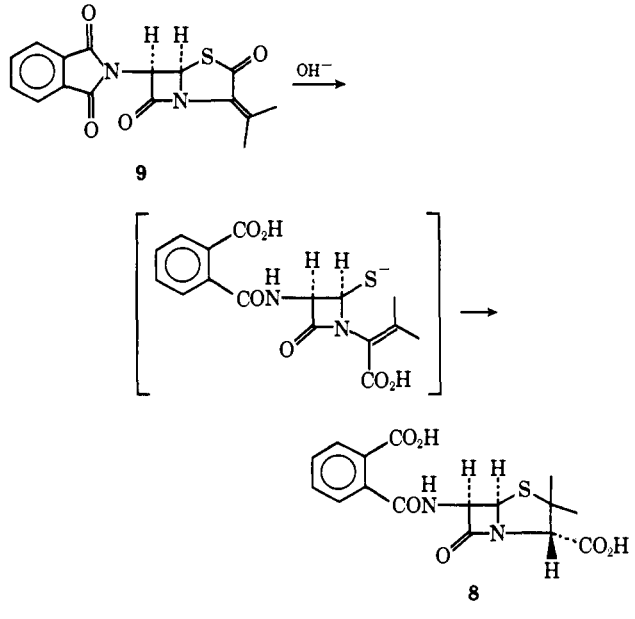
The isopropenyl double bond of **4** is generally inert to electrophilic reagents, it being recovered in high yield from reactions with bromine and permaleic acid. However, treatment of **4** with a peracid, *e.g.*, *m*-chloroper-

(10) S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. I. Wasson, *J. Amer. Chem. Soc.*, **91**, 7205 (1969).

Scheme I

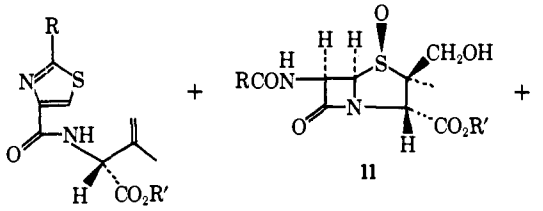


benzoic acid, in the presence of a catalytic amount of trifluoroacetic acid caused a smooth rearrangement to



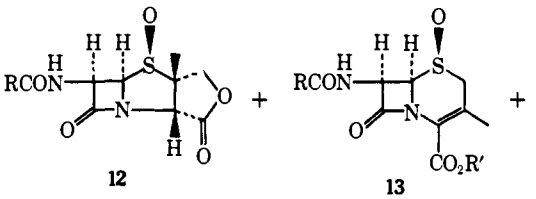
a mixture of products:[11] **2**,[12] **10**,[4,12] **11**,[13] **12**,[13] **13**,[12,14] **14**,[12,14] and **15**.[12,15]

4 → **2** +

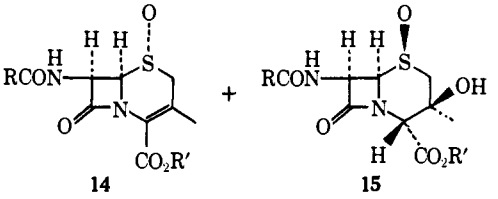


10

11



12 **13**

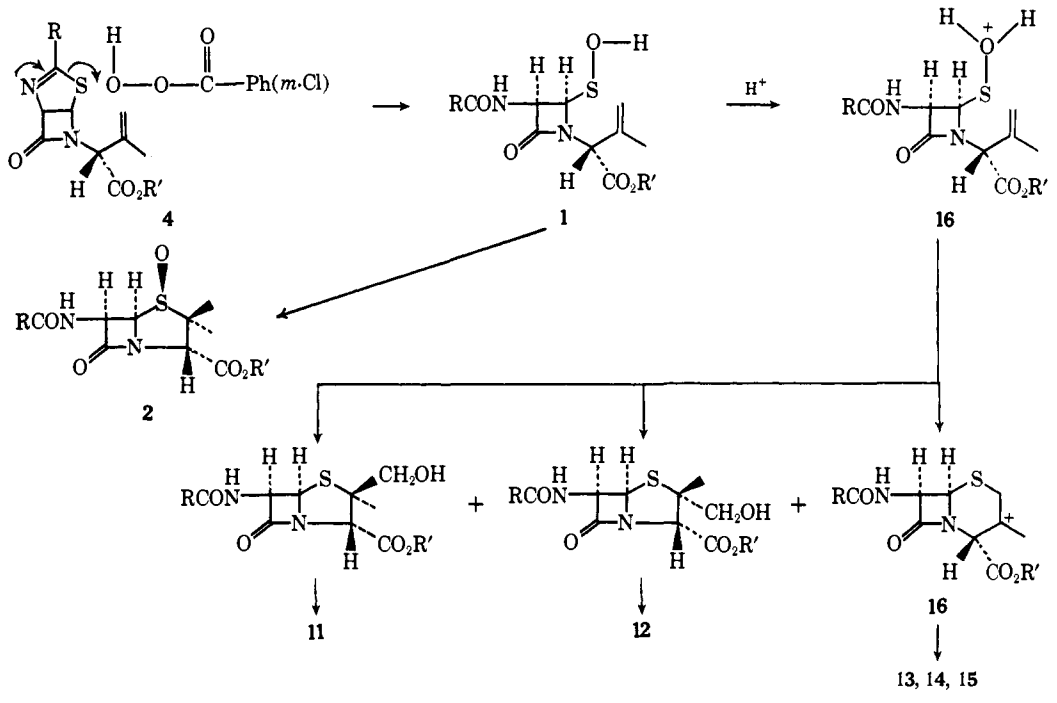


14 **15**

R = $PhOCH_2-$; R′ = CCl_3CH_2-

Thiazole **10**, formed by treatment of **4** with trifluoroacetic acid, has been observed previously.[4] We believe products **11–15** arise from an acid-catalyzed opening of the thiazoline ring to sulfenic acid **1** (Scheme II). Penicillin sulfoxide **2** is derived from the electrocyclic rearrangement of **1**.[3,16] Alternately, the sulfenic acid is protonated, changing the sulfur from a good nucleophile to an electrophile. Nucleophilic displacement at sulfur by the double bond gives hydroxymethylpenam, from which products **11** and **12** are derived, and the tertiary carbonium ion **16**, from which products **13**, **14**, and **15** are derived. A major distinction between this plethora of products and those obtained by Morin, *et al.*,[5] in the acetic anhydride rearrangement of **2** is that in this case we obtained both the 2β-hydroxymethyl and the 2α-hydroxymethyl penam derivatives (**11** and **12**), whereas, Morin, *et al.*,[5] obtained the 2β substitution product. We consider this distinction to be due to the different steric requirements of the leaving group at the sulfur atom, *i.e.*, $-{}^{+}OH_2$ *vs.* $-OCOCH_3$. Steric interaction with the amido side chain causes the acetoxy group to leave from the α face of the molecule and the double bond to approach on the β face. When the group leaving is $^{+}OH_2$, the steric interaction is considerably decreased and it is capable of leaving from both the α and β faces.[17] Finally, the reaction of the cephem and penam products with *m*-chloroperbenzoic acid was substantially faster than their formation, causing the isolated products to be the sulfoxides.

Scheme II



R = $PhOCH_2-$; R′ = CCl_3CH_2-

(11) The total yield and relative amounts of the products depended considerably on the solvent used.

(12) The structure was proven by comparison with authentic compound.

(13) Proof of the assigned structures was obtained by mass spectral fragmentation and nmr spectroscopy with application of aromatic induced solvent shifts and nuclear Overhauser effects.

(14) R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C*, 340 (1970).

(15) (a) G. E. Gutowski, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, *Tetrahedron Lett.*, 3433 (1971); (b) G. E. Gutowski, C. J. Daniels, and R. D. G. Cooper, *ibid.*, 3429 (1971).

(16) It is significant that **2** was only isolated when a nonpolar solvent (benzene) was used and then only as a minor product.

(17) A detailed discussion of the mechanism of the rearrangement of penicillin sulfoxides together with explanations for the product stereochemistry is the subject of a forthcoming publication.

Thus, it is chemically possible to transform **4** into both penam and cephem compounds. Therefore, we speculate that a derivative of type **7** could represent the divergent point in the biosynthesis of these two antibiotic structures.

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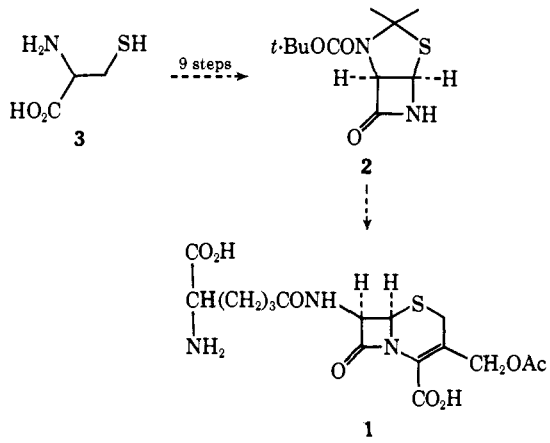
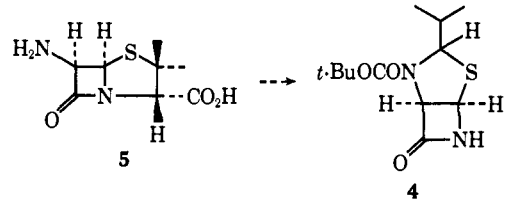
Structural Studies on Penicillin Derivatives. IX. Synthesis of Thiazolidine–Azetidinones

Sir:

A key intermediate in the total synthesis of cephalosporin C[1] (**1**) is the optically active thiazolidine–azetidinone **2** which was synthesized from L-cysteine **3** by a complex procedure involving at least nine steps. Extensive use of **2** has been made by Heusler and Woodward[2] in constructing analogs of cephalosporin C possessing modified dihydrothiazine ring systems. Heusler and Woodward have also reported[2] a more practical

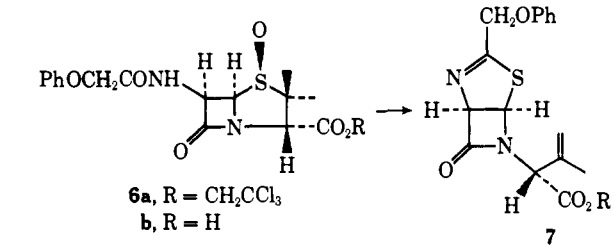


synthesis of a thiazolidine–azetidinone **4** from 6-aminopenicillanic acid (**5**). Penicillin has the obvious ad-

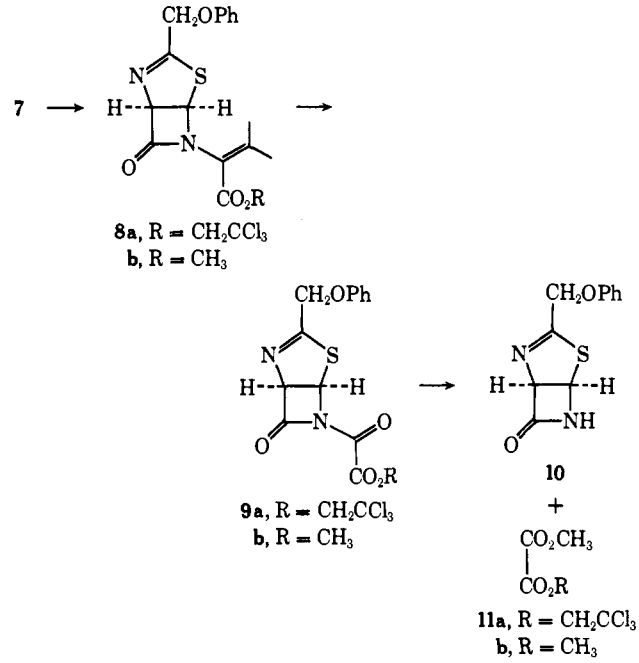


vantages of correct asymmetry and economic availability as a starting material for the synthesis of these types of intermediates, and we would like to report a simple, high-yielding, general process for the conversion of biosynthetic penicillins to thiazolidine–azetidinones.

We have recently reported[3] a novel rearrangement of the penicillin sulfoxide **6** to the thiazoline–azetidinone **7**.[3] This crystalline derivative can be isolated in yields of greater than 80%. The problem remaining



in conversion of **7** to an intermediate of type **4** is the removal of the five-carbon fragment. This was achieved by isomerization of the double bond of **7** with triethylamine to **8a** followed by ozonolysis in methylene chloride at −78° to yield the crystalline oxamide **9a**:[4] mp 98°; ν_{max} 1825 (β-lactam C=O), 1770 (oxamide C=O), and 1715 cm^{-1} (ester C=O). Cleavage of the oxamide function of **9a** with methanol containing a small amount of sodium methoxide gave the thiazoline–azetidinone **10** (70% yield from **7**) [mp 157–158°; nmr δ ($CDCl_3$) 5.01 (2 H, s, broad), 5.50 (1 H, d, J = 4 Hz), 6.07 (1 H, m), 6.50 (1 H, s, broad, exchangeable), and 6.9–7.4 (5 H, m); ir (mull) 1760 cm^{-1} (β-lactam C=O)] and the oxalate **11a**. A further reduction in the number



of operations was possible by direct rearrangement of penicillin sulfoxide **6b** using trimethyl phosphite as solvent. The major product after treatment of the reaction mixture with triethylamine was the methyl ester **8b**. Ozonolysis of **8b** followed by methanolysis gave **10** and dimethyl oxalate (**11b**). Reaction of **10** with aluminum–amalgam in moist ether gave in high yield the thiazolidine–azetidinone **12** [mp 147°; nmr δ ($CDCl_3$) 1.68 (3 H, d, J = 6 Hz), 4.62 (1 H, m), 5.19 (1 H, q, J = 3.5 Hz, 6 Hz), 5.52 (1 H, d, J = 3.5 Hz), and 6.0 (1 H, broad, exchangeable)] by reduction of the C=N bond and removal of the phenoxy group, giving phenol as a by-product. Reaction of **12** with phosgene and treatment of the chlorocarbonyl derivative **13** with *tert*-butyl alcohol gave the thiazolidine–azetidinone **14** [nmr δ ($CDCl_3$) 1.50 (9 H, s), 1.78 (1 H, d, J = 6 Hz),

(1) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966).
(2) K. Heusler and R. B. Woodward, German Offenlegungsschrift 1,935,607 (1970).
(3) R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, **92**, 2575 (1970).
(4) All new compounds gave satisfactory analytical data and mass spectra.