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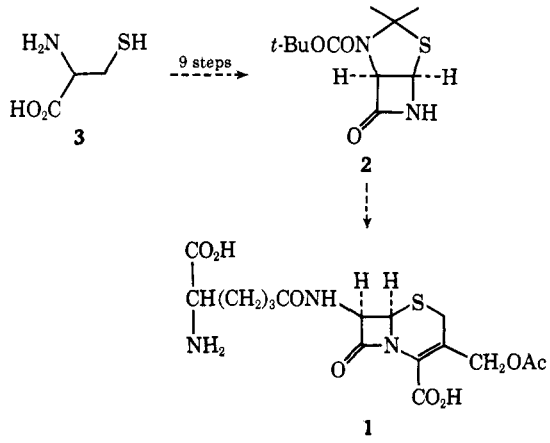
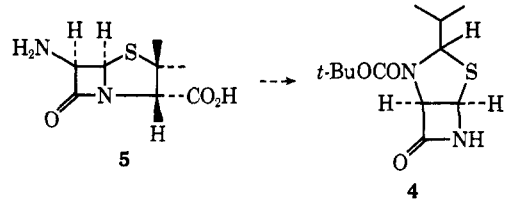
Structural Studies on Penicillin Derivatives. IX. Synthesis of Thiazolidine–Azetidinones

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

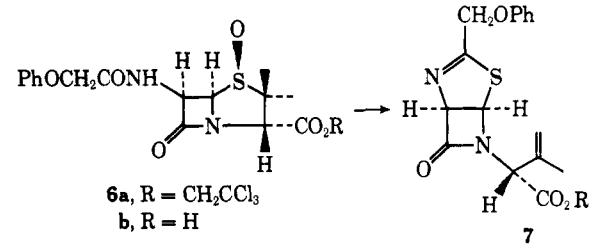


synthesis of a thiazolidine–azetidinone **4** from 6-aminopenicillanic acid (**5**). Penicillin has the obvious ad-

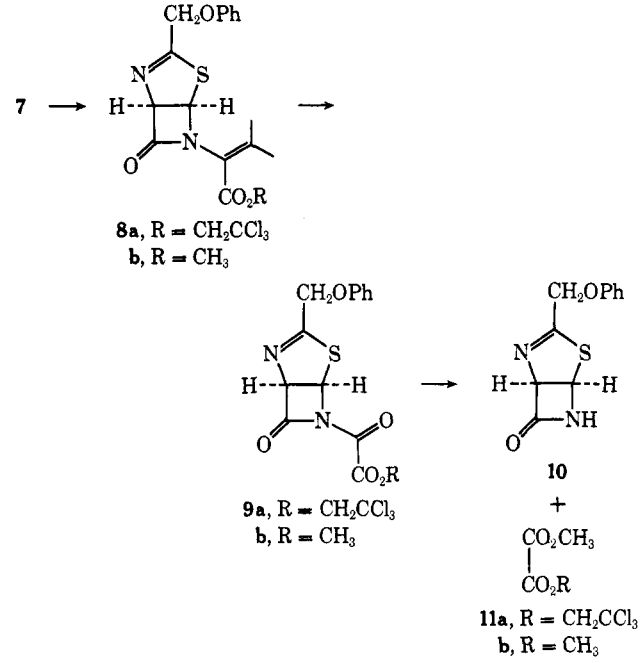


vantages of correct asymmetry and economic availability as a starting material for the synthesis of these types of intermediates, and we would like to report a simple, high-yielding, general process for the conversion of biosynthetic penicillins to thiazolidine–azetidinones.

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



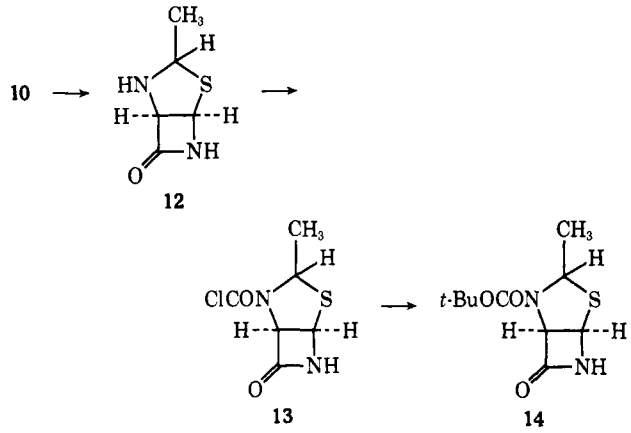
in conversion of **7** to an intermediate of type **4** is the removal of the five-carbon fragment. This was achieved by isomerization of the double bond of **7** with triethylamine to **8a** followed by ozonolysis in methylene chloride at −78° to yield the crystalline oxamide **9a**:[4] mp 98°; ν_{max} 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



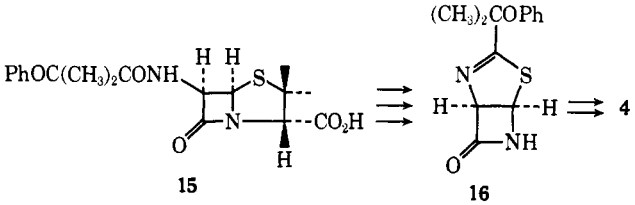
of operations was possible by direct rearrangement of penicillin sulfoxide **6b** using trimethyl phosphite as solvent. The major product after treatment of the reaction mixture with triethylamine was the methyl ester **8b**. Ozonolysis of **8b** followed by methanolysis gave **10** and dimethyl oxalate (**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.

4.99 (1 H, q, J = 6 Hz), 5.33 (1 H, d, J = 4 Hz), 5.73 (1 H, q, J = 4 Hz, 2 Hz), and 7.10 (1 H, broad, exchangeable)] analogous to that previously used in the synthesis of cephalosporin C.



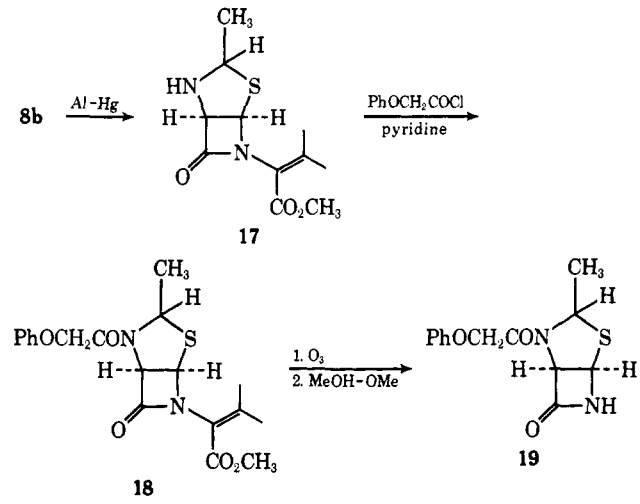
Repetition of this reaction sequence on α-methyl-α-phenoxyethylpenicillin (**15**) yielded the thiazoline **16** which on reduction and acylation yielded the thiazolidine **4** identical with that prepared by Heusler and Woodward.[2]

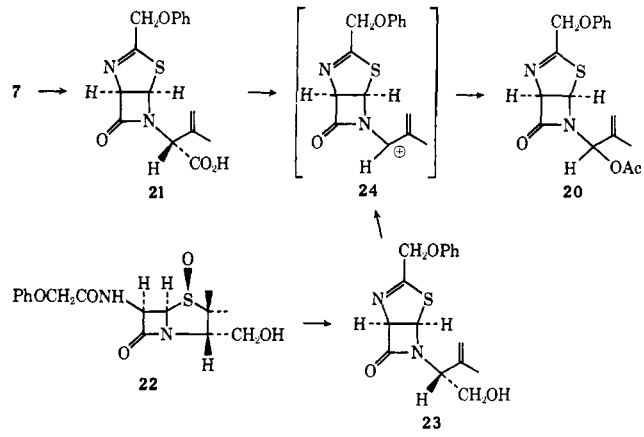


Removal of the five-carbon unit from thiazolidine–azetidinone derivatives could also be achieved. Thus aluminum–amalgam reduction of the thiazoline **8b** gave an excellent yield of the thiazolidine **17** [nmr δ ($CDCl_3$) 1.50 (3 H, d, J = 6 Hz), 1.92 (3 H, s), 2.19 (3 H, s), 3.77 (3 H, s), 4.40 (2 H, m, 1 exchangeable), 5.20 (1 H, broad, d, J = 4 Hz), and 5.73 (1 H, d, J = 4 Hz)], which could then be acylated with phenoxyacetyl chloride to yield **18** [nmr δ ($CDCl_3$) 1.65 (3 H, d, J = 6 Hz), 1.95 (3 H, s), 2.23 (3 H, s), 3.70 (3 H, s), 4.92 (2 H, s), 5.24 (1 H, q, J = 6 Hz), 5.70 (2 H, s), and 6.7–7.4 (5 H, m)].

Ozonolysis and methanolysis of **18** yielded the thiazolidine–azetidinone **19**: mp 135–137°; nmr δ ($CDCl_3$) 1.88 (3 H, d, J = 6 Hz), 4.94 (2 H, s), 4.95 (1 H, d, J = 4 Hz), 5.04 (1 H, d, J = 6 Hz), 5.93 (1 H, broad, d, J = 4 Hz), 6.9–7.4 (5 H, m), and 9.08 (1 H, broad, exchangeable); ir (mull) 1792 (β-lactam C=O) and 1700 cm^{-1} (amide C=O).

An alternate approach involving the acetoxy derivative **20** was also successful. Compound **20** [nmr δ ($CDCl_3$) 1.67 (3 H, broad, s), 2.06 (3 H, s), 4.88 (2 H, s), 5.03 (1 H, broad, s), 5.20 (1 H, broad, s), 5.54 (1 H, d, J = 4 Hz), 5.93 (1 H, d, J = 4 Hz), 6.36 (1 H, s), and 6.7–7.4 (5 H, m)] was synthesized in high overall yield by treatment of **7** with zinc in 90% acetic acid to obtain the acid **21**, followed by reaction of **21** with lead tetraacetate in benzene. An alternate route to **20** was developed from the penicillanyl alcohol sulfoxide **22** which was rearranged to the thiazoline **23** with trimethyl phosphite in benzene. Subsequent treatment of **23** with lead tetraacetate in benzene gave a quantitative yield of **20**. Formation of **20** in high yield from either **21** or **23** is not unexpected because of the stabilization of the incipient carbonium ion **24** by both the β-lactam nitrogen atom and the allylic double bond.





Hydrolysis of the acetoxy function of **20** using pH 7.6 phosphate buffer led to isolation of the thiazoline–azetidinone.[5] Unfortunately, the yield in the hydrolysis step was poor; however, we think that further work could improve this substantially.

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The Synthesis of 6,7-Diphenyl-3-thiabicyclo[3.2.0]heptatriene, a Thienocyclobutadiene

Sir:

Whereas 1,2-diphenylanthra[*b*]cyclobutadiene (**1**)[1] and the substituted naphtho[*b*]cyclobutadienes (**2a,b**),[2] have been isolated as relatively stable compounds, benzocyclobutadiene (**3**) and its derivatives have only

(1) M. P. Cava, *Chem. Soc., Spec. Publ.*, **21**, 163 (1967).
(2) M. P. Cava, B. Y. Hwang, and J. P. van Meter, *J. Amer. Chem. Soc.*, **85**, 4032 (1963); M. P. Cava and B. Y. Hwang, *Tetrahedron Lett.*, 2297 (1965).