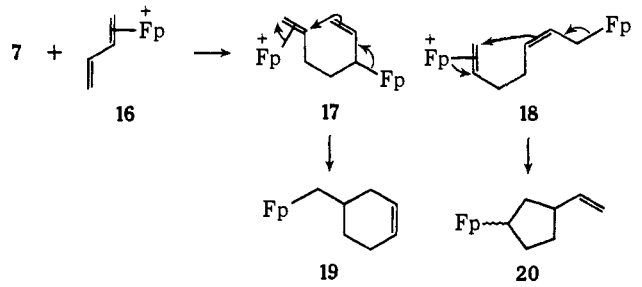
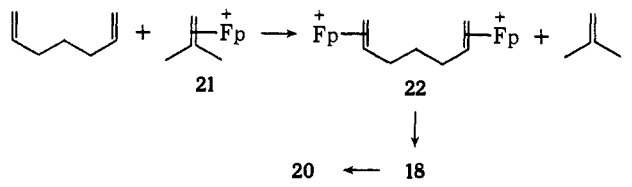
of carbocyclic rings. Thus, **7** reacts with the butadiene complex **16** to afford, after treatment with iodide, a mixture of cyclohexene and vinylcyclopentane complexes **19** and **20**, formed apparently *via* the intermediates **17** and **18** (40%).



The structure of **19** was established by independent synthesis through metallation of 4-hydroxymethylcyclohexene benzenesulfonate with the organometallic anion (Fp^-), while **18** and thence **20** can alternatively be obtained by exchange of the isobutylene complex (**21**)[10b] with 1,7-heptadiene, followed by treatment of the dication **22** with a molar equivalent of triethylamine.



Further elaborations and extensions of these reactions are being examined.

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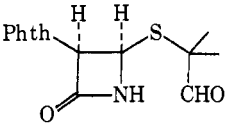
Removal and Displacement of the Thiazolidine Ring in Penicillin. II.[1] Selective Carbon–Sulfur Bond Cleavage

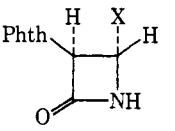
Sir:

Several methods have been reported for degrading the penicillin nucleus to monocyclic azetidin-2-ones.[2] We wish to report our progress in degrading **1**.[2a] Our studies, which extended over the past several years, have involved the reaction of **1** with chlorine. This reaction has recently been used by others to cleave the azetidine C–S bond of the penicillin nucleus.[2d] We have utilized this reagent to effect selective cleavage of the C–S bond on either side of the sulfur atom. This allows preparation of compounds **2** and **5**. In the latter case the C_4 side chain is removed while retaining the natural stereochemistry of the azetidine ring.

Direct chlorinolysis of **1**[3] as a suspension in CCl_4 using excess chlorine produced **2a**,[4,5] mp 142–144°, in



1



2a, X = Cl
b, X = OCH_3
c, X = OAc
d, X = SPh

nearly quantitative yield. The chloride underwent facile solvolytic displacement at room temperature. Methanol gave **2b**, mp 192–193°, and acetic acid produced **2c**, mp 187–189°. In addition to the nmr absorptions shown in Table I, **2b** and **2c** show methyl singlets at δ 3.5 and 2.2, respectively. The chloride **2a** also reacted with thiophenol in the presence of triethylamine to give **2d**, mp 212–213°. The spectral data indicate the integrity of the β-lactam and the trans relationship of the C_3 and C_4 protons in the predominant product. This method of cleaving the thioethyl side chain complements the method developed earlier in these laboratories based on displacement of the sulfone analog of **1**.[1]

Table I. Spectral Characteristics[a]

Compd	δ_{H_3}, δ_{H_4}[b]		$J_{3,4}$, Hz	Lactam CO, cm^{-1}
2a	5.6	6.0[c]	1.4[d]	1800
2b	5.3	5.4	1.5[d]	1790
2c	5.4	6.2	1.5[d]	1790
2d	5.1	5.3	2.4[d]	1785
3a	5.75	5.85	6.4	1825
3b	5.70	5.75	5.6	1805
4a	6.1		6.8[e]	1830
4b	5.9			1795
5a	5.2	5.6[f]	5.0	1790
5b	5.2	5.6[f,g]	4.8	1785
6a	5.6	5.7	6.0	1800
6b	5.2	5.5	3.5	1800
7	5.6	6.0	2.4	1810

[a] All compounds show absorption at δ 7.9–8.0 in the nmr and near 1770 and 1720 cm^{-1} in the ir due to the phthalimido group; nmr spectra are run in $CDCl_3$ and ir spectra in CH_2Cl_2. [b] Assignment of the lower field signal to H_4 can be made for **2a**, **5a**, and **5b** on the basis of coupling to the NH. Otherwise, assignment is ambiguous. [c] Noticeably broadened due to weak coupling to NH. [d] The coupling constants shown are for the predominant trans isomer. [e] Observed in C_6D_6. [f] Further split by NH with $J \simeq 1$ Hz. [g] Overlapping absorptions of isomers with chlorine cis and trans to sulfur.

Sodium borohydride reduction of **1** produced the corresponding alcohol, mp 196–197°, $[\alpha]D$ −6°, which was acylated smoothly in methylene chloride solution by trifluoroacetic anhydride in the presence of potassium carbonate. The product **3**, mp 148–149°, $[\alpha]D$ −125°, shows two singlets in the ^{19}F nmr spectrum 3.28 and

(1) Part I: J. C. Sheehan and C. A. Panetta, *J. Org. Chem.*, **38**, 940 (1973).

(2) (a) J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, **87**, 5468 (1965); (b) D. H. R. Barton, *Chem. Commun.*, 845 (1971); (c) R. D. G. Cooper, *J. Amer. Chem. Soc.*, **94**, 1018, 1021 (1972); (d) S. Kukolja, *ibid.*, **94**, 7590 (1972), and previous communications cited therein; (e) S. Wolfe, W. S. Lee, G. Kannengiesser, and J. Ducey, *Can. J. Chem.*, **50**, 2894 (1972); (f) M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Lett.*, 5097 (1972), and references therein; (g) J. H. C. Naylor, M. J. Pearson, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 57 (1973), and references therein.

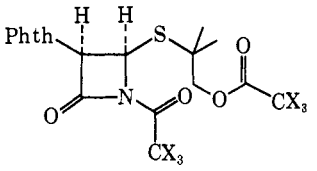
(3) Phth = phthalimido.

(4) Satisfactory analytical data have been obtained for all compounds unless otherwise noted.

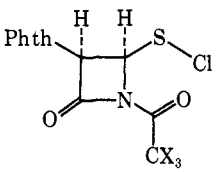
(5) The compounds **2** are cis–trans mixtures, but the trans isomer usually constitutes >85% of the mixture.

3.71 ppm downfield from external trifluoroacetic acid. While rearrangements are possible in the thioethyl side chain, the chemical shift of the methylene protons in **3a** (an AB system centered at δ 4.3 (J = 11 Hz)) indicates an unrearranged product. The *gem*-dimethyl groups appear at δ 1.45 and 1.35.

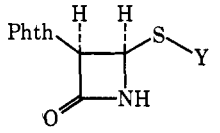
In contrast to **1**, treatment of **3a** with 2 equiv of



3a, X = F
b, X = H



4a, X = F
b, X = H

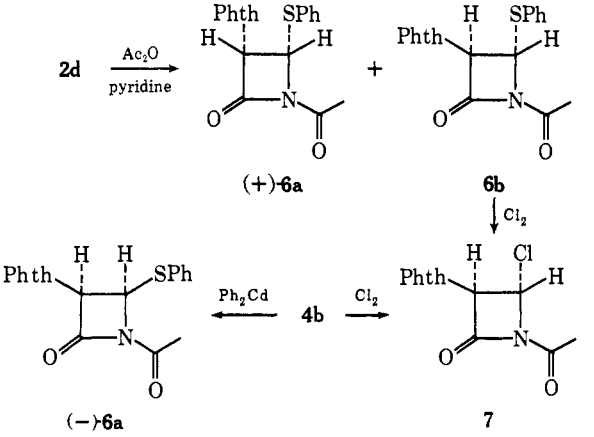


5a, Y = SPh
b, Y = 2-chlorocyclohexyl

chlorine in CH_2Cl_2 solution at room temperature produced a moderately stable sulfenyl chloride, **4a**. Apparently the *N*-acyl group inhibits participation of the nitrogen lone-pair electrons in cleavage of the azetidine C–S bond and makes cleavage of the tertiary C–S bond the favored pathway. The sulfenyl chloride was not obtained completely free of other cleavage products due to difficulty in crystallization and instability during chromatography. The ir spectrum of the crude product shows a high-frequency β-lactam carbonyl, indicative of the imidic system.[6] The ring protons appear as a singlet at δ 6.1 in $CDCl_3$ but become an AB system centered at δ 5.25 in C_6D_6. The yellow oil liberated iodine from sodium iodide in acetic acid and reacted rapidly at room temperature with thiophenol or cyclohexene, reactions typical of a sulfenyl chloride.[7] When the products of the latter two reactions were chromatographed on Florisil, the aliphatic cleavage products eluted rapidly with CH_2Cl_2. The products **5a** and **5b**, respectively, came off the column with CH_2Cl_2–ethyl acetate, 9:1. Apparently, the Florisil catalyzes the removal of the highly labile trifluoroacetyl group by traces of moisture or ethanol. The disulfide **5a**, mp 104–107°, $[\alpha]D$ −76°, was obtained in 75% yield and shows a normal β-lactam carbonyl absorption and an AB system characteristic of a cis-3,4 disubstituted ring. Similarly, **5b**, mp 164–166°, was obtained in 85% yield. The absorption of the C_4 proton in the nmr spectrum of **5b** appears as two overlapping signals (each a doublet of doublets) indicating that the compound is a mixture of the two possible isomers with chlorine cis or trans to sulfur on the cyclohexane ring. An excess of chlorine converts **5a** to **2a** in 70% yield.

A similar series of reactions has been performed utilizing the diacetyl analog **3b**, prepared by treating the alcohol with acetic anhydride–pyridine at 50° after the method of Heusler.[6] This compound was obtained as an oil, $[\alpha]D$ −141°, which shows an AB system centered at δ 4.0 (J = 11 Hz) and four three-proton singlets at δ 2.5, 1.9, 1.6, and 1.2 as well as the absorptions listed in Table I. Two equivalents of chlorine reacted with **3b** to give **4b**, an oil which resisted purification and which also shows an anomalous two-proton singlet for the azetidine ring protons, both in $CDCl_3$ and C_6D_6. Reactions of **4b** with thiophenol and cyclohexene appear to parallel those of **4a**, except that the *N*-acetyl group remains intact during chromatography. The products are oils which have not been obtained analytically pure.

In an attempt to establish more definitely the structure of **4b**, treatment with diphenylcadmium in tetrahydrofuran gave **6a**, mp 149.5–152°, $[\alpha]D$ −199°, in low yield (*ca.* 3%). The enantiomer of **6a**, mp 150–153°, $[\alpha]D$ 174°, was formed by acetylation of **2d**, followed by chromatographic separation of the two isomers. Apparently, the major portion of the cis isomer from this reaction arises from epimerization at C_3 with a small amount due to the fact that **2d** contains some cis isomer. Compound **6b** can be observed to epimerize in pyridine at 50°, but epimerization was not observed for **2d** or **3b**. The fact that both reaction pathways lead to optically active products rules out any intermediate (such as a 3,4-dehydroazetidin-2-one) in which both asymmetric centers are destroyed. Compound **4b** reacts with excess chlorine to give **7**, mp 167–168°, also obtainable by chlorinolysis of **6b**.



(+)-**6a** **6b** (−)-**6a** **7**

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(6) K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972).
(7) For a review, see I. B. Douglass in "Organic Sulfur Compounds," N. Kharasch, Ed., Vol. I, Pergamon Press, New York, N. Y., 1961, Chapter 30.

Solvent Isotope Effects and the Mechanism of Chymotrypsin Action[1]

Sir:

A recent communication[2] reported that the solvent isotope effect on the deacetylation of acetyl-α-chymo-

(1) This research was supported by the National Science Foundation through Grant No. GP-36004X.
(2) E. Pollock, J. L. Hogg, and R. L. Schowen, *J. Amer. Chem. Soc.*, **95**, 968 (1973).