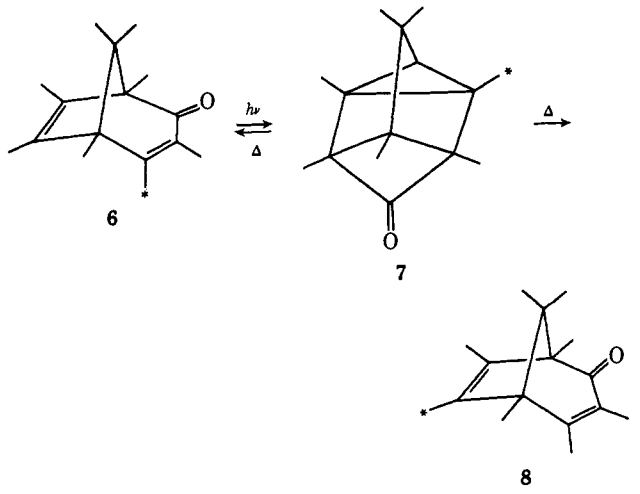


6 7 8

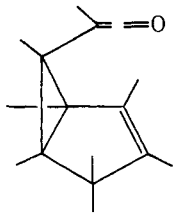
M − CO became the base peak. The data in Table I suggest that the M − CH_3 peak arises mainly from

Table I. Selected Peaks in the Mass Spectrum of **4**

Ionizing voltage, eV	Relative peak intensities, *m/e* 232	217	204
70	47	100	20
20	32	70	100
17.5	30	50	100
15	35	35	100
13	56	16	100

3, and the M − CO peak mainly from **4**.

We have thus far been unable to trap the ketene **9** with a nucleophile. Irradiation of **3** in ether containing a large excess of dimethylamine, either at room temperature or at −190°, or in methanol under similar conditions, gave only **4**. But direct evidence for the intermediacy of **9** was obtained when a solution of **3**



9

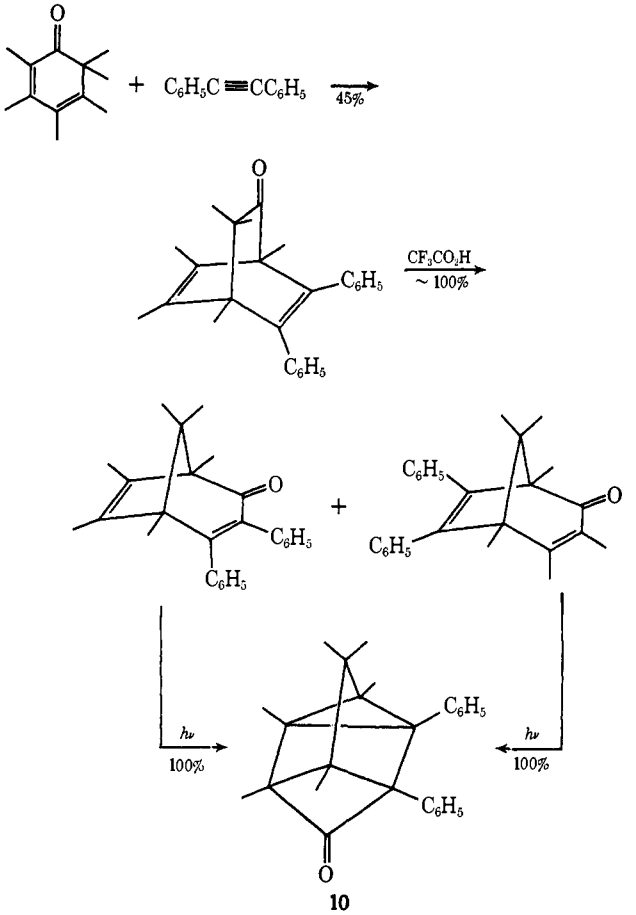
in pentane was frozen as a thin solid film and irradiated in an infrared cell[7] at about −190°. The expected sharp ketene absorption at 2110 cm^{-1} appeared quite quickly; however, even slight warming resulted in rapid conversion of the ketene to **4** (1760-cm^{-1} band). There is, therefore, no doubt that the reaction proceeds *via* a ketene intermediate.

Interconversions of the type **3** ⇌ **4** are probably quite general if the ring systems are highly substituted. For example, we have prepared the diphenyl analog **10** in essentially quantitative yield after the first step, by the following reaction sequence.[8,9]

(7) A Hanovia UV 100 irradiation system was used as the energy source.

(8) The first step and preliminary work on the second step were carried out by T. Kakihana, M.S. Thesis, Michigan State University, 1966.

(9) Experimental conditions and structural evidence will be presented in a full paper; they are unexceptional.



10

The accelerating effect of alkyl groups on the intramolecular cycloaddition of the type **9** → **4** is reminiscent of similar substituent effects on the cyclization of diene ketenes to conjugated cyclohexadienones[10] and bicyclo[3.1.0]hexenones.[11,12]

The parent hydrocarbon of the tetracyclic ring system present in **4** and **10** has been reported,[13] but we believe this is the first preparation of functional derivatives of the system.

We are exploring the scope of the intramolecular cycloaddition reaction described, as well as the chemistry of the interesting ring system which it generates.

Acknowledgment. We are indebted to the National Science Foundation and the National Institutes of Health for their generous support.

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Electrophilic Opening of the Thiazolidine Ring in Penicillins

Sir:

In recent years the selective opening of the thiazolidine ring of the penicillin nucleus in which the azeti-

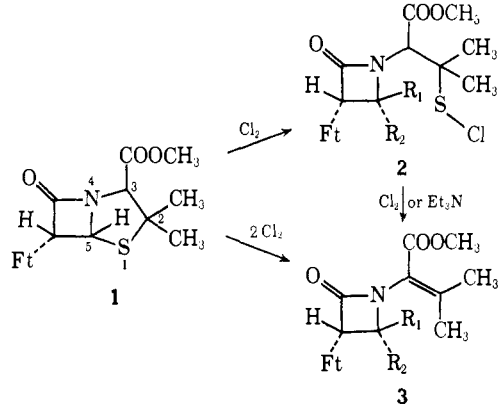
dinone moiety remains intact has been accomplished by several methods. The S_1–C_2 bond cleavage of the penam system and the subsequent rearrangements to anhydropenicillin,[1,2] bicyclic oxazoline azetidinone compounds,[3,4] fused thiazoline azetidinone derivatives,[5] monocyclic thioacetyl azetidinone compounds,[6] and ring-enlarged cepham and cephem systems[7,8] have been observed. The C_3–N_4 bond cleavage of the thiazolidine ring has also been reported resulting in the synthesis of a wide variety of versatile monocyclic azetidinone derivatives.[9,10]

The research reported here is concerned with the cleavage of the S_1–C_5 bond of the thiazolidine ring in penicillins. We have found that the reaction of penicillin esters with electrophiles opens the S_1–C_5 bond without disruption of the azetidinone ring. Positive halogen is used as an electrophile, and two different types of products are obtained depending on the amount of halogen used. With an equivalent amount of halogen, the corresponding azetidinone sulfenyl derivatives **2a** and **2b** are obtained in almost quantitative yield. However, when 2 equiv of electrophile is employed, the olefinic azetidinone compounds **3a** and **3b** are isolated in high yield.

Treatment of methyl 6-phthalimidopenicillanate (**1**) with 1 equiv of chlorine or sulfuryl chloride in carbon tetrachloride at room temperature for 30 min gives a mixture of two isomeric compounds. The isomers, present in the ratio *ca.* 4:1, are isolated by chromatography over silica gel or by fractional crystallization from benzene. The major product is obtained as yellow prisms, mp 158–160°, $[\alpha]D$ +36.4° ($CHCl_3$), and the structure **2a** is assigned on the basis of the following data. The compound is capable of liberating iodine from potassium iodide.[11] The ir spectrum ($CHCl_3$) shows peaks at 1800 (β-lactam CO), 1785 and 1735 (phthalimido CO), and 1750 cm^{-1} (ester CO). The nmr spectrum ($CDCl_3$) shows a six-proton singlet at 103.5 ascribable to the two methyl groups attached to a saturated quaternary carbon, a peak at 232 for the ester methyl group, a sharp one-proton peak at 274.5 corresponding to H-3, two doublets at 332.5 and 364 with the coupling constant J = 2.0 Hz indicating the trans stereochemistry of the β-lactam protons,[12] and a peak at 471.5 Hz for the four aromatic protons.

The minor isomer **2b**, yellow prisms, mp 145–147°, has an ir spectrum nearly identical with that of **2a** and an nmr spectrum similar except for the position and coupling constant of the β-lactam protons. These are present as doublets at 341 and 378.5 Hz, and the cis relationship of the hydrogens on the four-membered ring is affirmed on the basis of the coupling constant (J = 4.0 Hz).[12]

The reaction of **1** with 2 equiv of chlorine in carbon tetrachloride at −76° for 1 hr and at room temperature for an additional 1 hr affords a mixture of trans and cis isomers **3a** and **3b** which are isolated by chromatography over silica gel. These compounds can also be prepared directly from **2** with 1 equiv of chlorine under the same reaction conditions, or by treatment of **2** with triethylamine in methylene chloride. Structural assignments have been made on the basis of elemental analysis and spectral properties. Compound **3a**, a colorless foam, $[\alpha]D$ −131.3° ($CHCl_3$), gives a peak in the



a, Ft = phthalimido; R_1 = Cl; R_2 = H

b, Ft = phthalimido; R_1 = H; R_2 = Cl

spectrum at m/e 362, corresponding to $C_{17}H_{15}ClN_2O_5$,[13] and major fragmentation peaks at m/e 326 (M^+, HCl), 303 (M^+, $COOCH_3$), 299 (M^+, CO, Cl), 267 (M^+, $COOCH_3$, HCl), and 239 (M^+, $COOCH_3$, HCl, CO). The ir spectrum (KBr) shows peaks at 1800 (β-lactam CO), 1780 and 1725 (phthalimido CO), and 1725 cm^{-1} (ester CO). The presence of an isopropylidene group is confirmed by absence of an H-3 signal in the nmr spectrum ($CDCl_3$) and by three-proton singlets from unsaturated methyl groups (126 and 140 Hz). The trans arrangement of β-lactam protons for **3a** is established by doublets at 335 and 375 Hz and the size of the coupling between these protons (J = 1.8 Hz). The cis isomer **3b**, a colorless amorphous solid, shows similar ir and mass spectra to those of **3a**, but differs in the stereochemistry of the β-lactam protons. Doublets at 342.5 and 371 Hz and their coupling constant (J = 4.0 Hz) establish that vicinal protons are cis oriented.

The reaction of **1** with positive halogen presumably proceeds through initial formation of sulfonium salt intermediates **4** and **6** and subsequent C–S bond cleavage.[14] The intermediate **4** or **5** is susceptible to nucleophilic attack by chloride ion, the result being the nucleophilic displacement of the sulfonium ion by chloride and the formation of sulfenyl chlorides **2a** and **2b**.[15,16] In these reactions the departure of the sulfonium group and stabilization of the formed car-

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(14) H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, **78**, 5008 (1956); H. Kwart and L. J. Miller, *ibid.*, **80**, 884 (1958).
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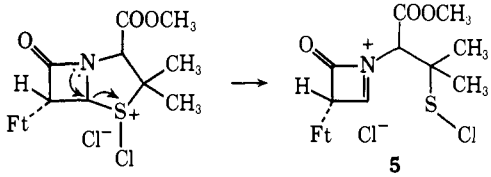
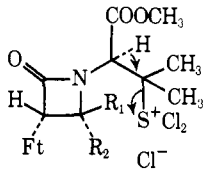
(16) F. G. Bordwell and B. M. Pitt, *ibid.*, 77, 572 (1955).

bonium ion is assisted by electron delocalization of the unshared electron pair of the nitrogen atom as depicted by **4** and **5**.[17] Theoretically, a nucleophilic chloride could approach the stabilized carbonium ion **5** from either side giving trans and cis isomers in equal amounts. However, in the case of **5** a bulky phthalimido group directs the nucleophilic displacement and as a result the trans and cis isomers **2a** and **2b** are formed in the ratio of *ca.* 4:1. The new olefin-forming reaction can be explained similarly by the good leaving characteristics of the dichlorosulfonium group and β elimination of hydrogen, as illustrated by **6.**



4 **5**



6

Further investigation of these reactions and utilization of described intermediates in eventual syntheses of new β-lactam compounds are in progress and will be reported subsequently.

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A Stereoselective Synthesis of 6-Phthalimido-5-epipenicillanates

Sir:

Structural studies of naturally occurring penicillins have shown that the bicyclic skeleton of the penicillin molecule is formed by joining azetidinone and thiazolidine rings in such a fashion that asymmetric carbon 5 has the *R* configuration. However, the fused bicyclic system can also exist with C-5 having the *S* configuration, and such penam systems may be called 5-epi- or 5*S* penicillins. In addition to the asymmetric center at C-5, the penicillin structure contains two asymmetric carbon atoms, C-3 and C-6, and eight stereoisomeric forms are possible. Thus far only penicillin V (natural) and its enantiomer, synthesized by Sheehan and Henery-Logan,[1] and 6-epipenicillin V, obtained by Bose, *et al.*,[2] have been accessible. Recently, 6-epipenicillins have also been prepared by several groups of investigators.[3-5]

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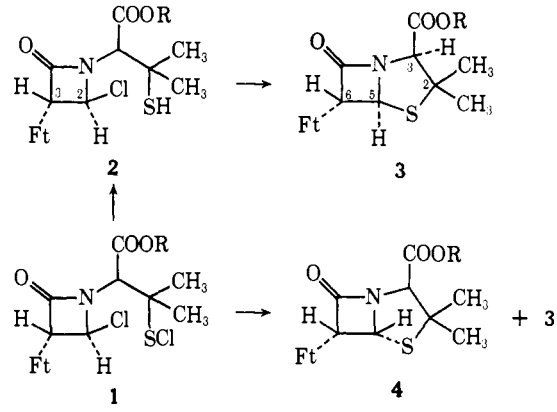
The preceding communication[6] describes a method for preparing monocyclic azetidinone derivatives which have now been employed successfully in the synthesis of the hitherto unknown 5-epipenicillanates (**3**). Penicillanates (**4**) having the natural configuration have also been obtained in this sequence.



2 **3** **1** **4**

Ft = phthalimido
a, R = CH_3
b, R = $CH(C_6H_5)_2$
c, R = H

Reaction of methyl 2-chloro-α-(1-chlorothio-1-methylethyl)-4-oxo-3-phthalimido-1-azetidineacetate (**1a**) with 1 equiv of stannous chloride dihydrate in hot dioxane for 1 hr affords a mixture of **3a** and **4a** in 74% yield. The nmr spectrum shows that the compounds are present in the ratio of *ca.* 5:1. The diastereomers are separated by chromatography or by crystallization from methyl ethyl ketone or acetone. Methyl 6-phthalimido-5-epipenicillanate (**3a**) is isolated as colorless prisms, mp 174–175°, $[\alpha]D$ −192° ($CHCl_3$), in >50% yield.[7] The substance has ir maxima ($CHCl_3$) at 1795 (azetidinone CO), 1785 and 1733 (phthalimido CO), and 1752 cm^{-1} (ester CO); its mass spectrum is similar to **4a** and shows, in addition to the molecular ion at *m/e* 360, characteristic peaks at 332 (M^+, CO), 301 (M^+, $COOCH_3$), 273 (M^+, CO, $COOCH_3$), and 246 (M^+, HCN, CO, $COOCH_3$). The nmr spectrum ($CDCl_3$) is entirely in agreement with structure **3a**, since two geminal dimethyl singlets at 90 and 102, a methyl ester singlet at 231, a sharp H-3 peak at 234, doublets at 327 and 334 (J = 2.0 Hz) for the trans arrangement of azetidinone protons, and a signal at 471 Hz for the aromatic protons are indicated. Compound **4a**, mp 177–178°, $[\alpha]D$ +291° ($CHCl_3$), is isolated as the minor constituent and is identical with an authentic sample.[8]

When **1a** is treated with *anhydrous* stannous chloride in tetrahydrofuran at room temperature for 2 hr, only 5-epipenicillanate **3a** is obtained. This result indicates the high stereoselectivity of reductive cyclization. However, the reaction of **1a** with stannous chloride *dihydrate* under the above conditions gives the reduced product **2a**, mp 156–157°, which is subsequently cyclized to **3a** with anhydrous stannous chloride in high yield. Apparently in the presence of water, only

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