Table II. Squared Correlation Matrix for Variables Pertaining to Equation 3

	MR-L	MR-S	π-MR-L	π-MR-S	I-1	I-2
MR-L	1.00	0.06	0.29	0.04	0.00	0.03
MR-S		1.00	0.07	0.50	0.00	0.01
π-MR-L			1.00	0.48	0.00	0.02
π-MR-S				1.00	0.00	0.02
I-1					1.00	0.02
I-2						1.00

site in chymotrypsin is not typically hydrophobic is supported by the analysis of Dickerson and Geis.[26] The "hydrophobic" pocket in chymotrypsin is circumscribed by the following two peptide sequences:

Gly Ala Ser Gly Val Ser Ser Cys Met
184 185 186 187 188 189 190 191 192

Ilu Val Ser Trp Gly Ser Ser Thr Cys Ser Thr Ser Thr Pro Gly Val
212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227

The vast majority of these residues are hydrophilic, not hydrophobic; thus, correlation with MR can be used to characterize nonhydrophobic enzyme space as π can be used for hydrophobic space.[27]

Equation 3 does establish the fact that it is possible to construct QSAR for stereoisomers by taking into account the type of space into which substituents fall. We believe that the approach used in formulating eq 3 should be generally applicable to problems involving stereoisomers.

Registry No.—α-*N*-Nicotinyl-L-4-nitrophenylalanine ethyl ester, 58816-65-2; L-4-nitrophenylalanine, 949-99-5; L-4-nitrophenylalanine ethyl ester HCl, 58816-66-3; L-4-nitrophenylalanine ethyl ester, 34276-53-4; nicotinyl azide, 4013-72-3; α-*N*-nicotinyl-L-4-nitrophenylalaninamide, 58816-67-4; α-*N*-nicotinyl-L-alanine ethyl ester, 58816-68-5; ethyl alaninate, 3082-75-5; α-*N*-nicotinyl alaninamide, 53503-62-1; α-*N*-benzoyl-4-nitrophenylalanine ethyl ester, 58816-69-6; α-*N*-benzoyl-4-aminophenylalanine ethyl ester, 58816-70-9; α-*N*-benzoyl-L-4-methanesulfonylamidophenylalaninamide, 58816-71-0; methanesulfonyl chloride, 124-63-0.

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(1) (a) This investigation was supported by Public Health Service Research Grant CA-11110 from the National Cancer Institute and the Sankyo Co. of Tokyo, Japan; (b) Visiting Scientist from the Sankyo Co.
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Ring Opening of Aziridine Phosphonates. Correlation of Structure, Nuclear Magnetic Resonance Spectra, and Reactivity[1a]

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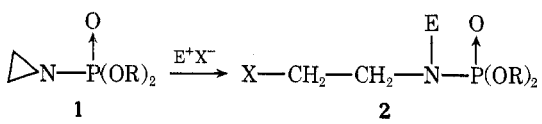
The ring opening of several dimethyl *N*-aziridinylphosphonates **3** with Cl_2 and HCl was studied. The reaction was found to be stereospecific and in most cases regiospecific. Conformational preferences in these compounds could be correlated with 1,3 P–H (PNCCH) coupling constants and with reactivity in ring opening.

The importance of aziridines as well as their N-phosphorylated derivatives in biological systems is well documented.[2] It is generally assumed that the cytotoxic behavior of such compounds is due to their ability to undergo ring opening by nucleophilic sites of enzymes.

The ring opening of unsubstituted aziridine phosphonates of type **1** to **2** with electrophilic reagents (E^+X^-) including

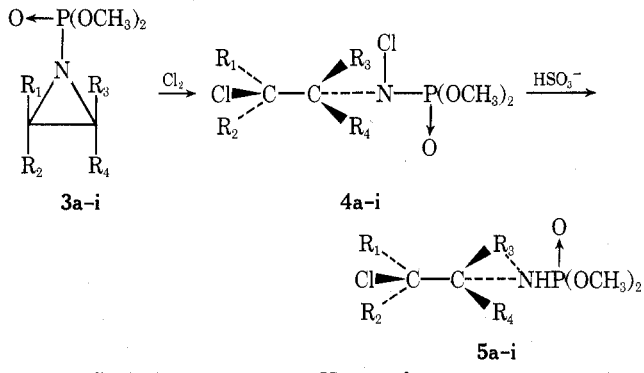


1 **2**

carboxylic acids, chlorine, and alkyl halides has been investigated by Russian chemists.[3a] Related *N,N*-dialkylaminoaziridinyl phosphoric amides react similarly.[3b]

In this study we are reporting on the chlorination of several ring substituted aziridine phosphonates **3** in an effort to determine the factors which influence the stereochemistry, regiochemistry, and the rate of ring opening.

Results and Stereochemistry. The reaction of dimethyl *N*-aziridinylphosphonates **3a–i** with chlorine in CCl_4 solution at 0–5 °C leads to dimethyl *N*-chloro-*N*-(β-chloroethyl)phosphoramidates **4a–i** in high yield. These *N*-chloro compounds cannot be purified effectively, but are reduced

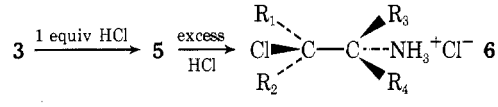


3a-i 4a-i 5a-i

a, $R_1 = C_6H_5$; $R_2 = R_3 = R_4 = H$
b, $R_1 = C_6H_5$; $R_4 = CH_3$; $R_2 = R_3 = H$
c, $R_1 = C_6H_5$; $R_3 = CH_3$; $R_2 = R_4 = H$
d, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
e, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
f, $R_1 = R_2 = R_3 = H$; $R_4 = C(CH_3)_3$
g, $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
h, $R_3 = R_4 = CH_3$; $R_1 = R_2 = H$
i, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$

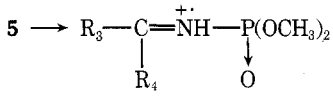
with $NaHSO_3$ in methanol[4] and the dimethyl *N*-(β-chloroethyl)phosphoramidates **5a–i** characterized by elemental analysis, spectra, and chemical conversions.

Ring opening of the aziridine derivatives **3** with 1 equiv of HCl in ether produces the identical phosphoramidates **5**. If an excess of HCl is employed cleavage of **5** takes place and the corresponding β-chloroethylamine hydrochlorides **6** are isolated.[4]

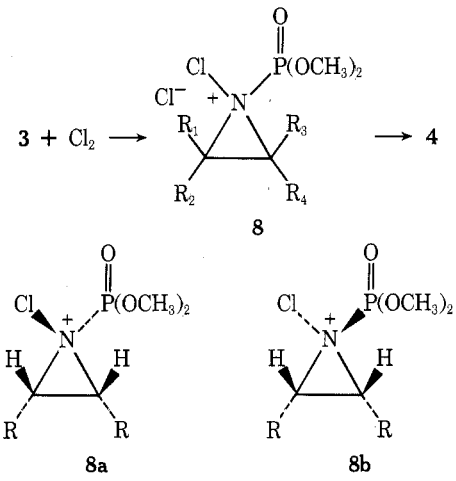


The stereochemical identity of **5** and **6** provides proof that the ring opening of **3** occurred in a stereospecific manner. Thus, **3b** (trans) produces only the erythro diastereomer **5b,** whereas the cis isomer **3c** leads exclusively to the threo product **5c.** Proof of trans ring opening is provided by the hydrolysis of **5d** and **5e** to the known erythro and threo β-chloroethylamine hydrochlorides **6d** and **6e,** respectively.

Regiochemistry. The spectral properties of the products **4** and **5** (Table I) indicate that ring opening of the aziridine phosphonates **3** occurs in a regioselective manner. In most cases attack by the nucleophile takes place at the most highly substituted carbon atom. Exceptions are the aziridines **3g** and **3h,** which give mixtures of products in the reaction with chlorine (**3h** also gives a mixture with HCl), and **3f,** in which ring opening occurred in the opposite regiochemical sense. The mass spectra of **5** showed base peaks resulting from cleavage α to N, confirming the regiochemical assignment.[5]



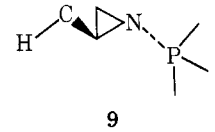
Mechanism. The following mechanism is most plausible. Attack of electrophilic chlorine on the nitrogen electron pair leads to intermediate **8** which is opened from the back side by chloride ion (stereospecific trans ring opening). For most of the aziridines studied there are two possible configurational intermediates, **8a** and **8b.** Of these, **8b** should be highly favored since chlorine is expected to have a much smaller steric requirement than the phosphonate group. For the same reason the phosphonate is expected to occupy the least hindered configuration in **3.** Since it is reasonable to assume that inversion about the nitrogen is rapid in phosphorylated aziridines **3,**[6] the relative proportion of **8a** and **8b** will depend on the free energies of the transition states leading to their formation. The results indicate that the chlorine molecule prefers



8 8a 8b

to approach the aziridine ring from the most hindered side forming the more stable isomer **8b.** Hence, the aziridine is chlorinated from its most stable conformation. It follows that if the aziridine has bulky cis groups as in **3c** or **3f** it chlorinates more slowly since the chlorine must enter cis to these groups. This was borne out experimentally. The relative rate of chlorination of **3a:3b:3c** was 460:17:1. **3f** was also chlorinated very slowly.

Conformations and Long-Range P–H Coupling. Information on the conformational preferences in simple phosphorylated aziridines **3** may be obtained frrom their NMR spectra[7] (Table II). Their basic NMR features have been discussed elsewhere.[6] In addition, we have noticed for the $C-CH_3$ groups in **3** long-range $^{31}P-^{1}H$ coupling which depends on certain stereochemical features. For instance, J_{PH} values of 0.6 Hz were observed for aziridine phosphonates in which the phosphorus function is expected to be cis or trans to the methyl groups with equal facility (as in **3d, 3h,** and **3j**). These were verified by ^{31}P decoupling.[8] Aziridines which have two cis groups (as in **3c, 3e,** and **3l**) show larger couplings, generally 1.2–1.6 Hz. This may be rationalized in terms of a conformational preference leading to the well-known "W" effect.[7] The phosphorus and one hydrogen on the methyl group can be in a "W" conformation only when they are on opposite sides of the ring as shown in **9.** This prerequisite is met when the methyl is found on the more substituted side of the aziridine ring causing the phosphorus to be trans to it. Attempts to find a correlation for the ring protons failed. A related compound, *N*-azetidinyltriphenylphosphonium iodide (**10**), prepared



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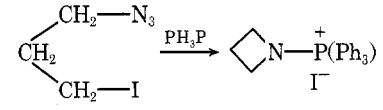

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from 1-azido-3-iodopropane, also showed an abnormally large four-bond coupling constant (4.5 Hz). This could be a result of a similar conformational bias enhanced by the availability of two σ bond pathways to transmit nuclear spin.

Experimental Section

The aziridine phosphonates, with the exception of **3f** described below, were synthesized from alkenes by IN_3 addition and reaction with trimethyl phosphite, a general method described elsewhere.[9] All compounds (with the exceptions of compound **4** noted in the text and of **5c,** which could not be obtained crystalline) had satisfactory (±0.3%

Table I. Physical Properties of *N*-(β-Chloroethyl) Phosphoramidates 4 and 5

Compd	Yield, %	Mp, °C	NMR spectra, τ (CCl_4)
4a	100		2.63 (m, 5), 4.84 (broad t, J = 7), 4.0–4.4 (m, 2), 6.30 (d, 3, J = 11), 6.63 (d, 3, J = 11)
4b	100		2.6 (m, 5), 5.17 (d, 1, J = 10), 5.3–5.9 (m, 1), 6.39 (d, 3, J = 11), 7.12 (d, 3, J = 11), 8.41 (d, 3, J = 6)
4c	100		2.64 (broad s, 5), 5.09 (d, 1, J = 10), 5.2–5.9 (m, 1), 6.18 (d, 3, J = 11), 6.24 (d, 3, J = 11), 9.00 (d, 3, J = 6)
4d	92		6.22 (d, 6, J = 11), 5.9–6.4 (m, 2), 8.42 (d, 3, J = 6), 8.57 (d, 3, J = 6)
4e	94		6.20 (d, 3, J = 11), 6.22 (d, 3, J = 11), 5.6–6.4 (m? 2), 8.43 (d, 3, J = 6), 8.58 (d, 3, J = 6)
4f	100		6.28 (d, 3, J = 11), 6.29 (d, 3, J = 11), 5.9–6.4 (m, 3), 8.93 (s, 9)
4g	100		5.90 (q, 1, J = 7), 6.23 (d, 3, J = 11), 6.24 (d, 3, J = 11), 8.33 (s, 6), 8.58 (d, 3, J = 7)
4h, 4i	100		6.0–6.5, 8.32, 8.52, 8.80
5a	52[a] 69[b]	67–69	2.67 (m, 5), 5.12 (t, 1, J = 7), 5.3–5.9 (broad, 1, NH), 6.35 (d, 3, J = 11), 6.50 (d, 3, J = 11), 6.6–6.9 (m, 1)
5b	54	95–97	2.7 (m, 5), 5.00 (d, 1, J = 5), 3.8–4.2 (broad, 1, NH), 4.1–4.7 (m, 1, buried), 4.37 (d, 3, J = 11), 4.57 (d, 3, J = 11), 8.82 (d, 3, J = 6)
5d	32	67–68	5.6–6.1 (broad, 1, NH), 6.4–7.0 (m, 1), 6.34 (d, 6, J = 11), 8.48 (d, 3, J = 6), 8.79 (d, 3, J = 6)
5e	55[a] 99[b]	84–86	5.0–5.8 (broad, 1, NH), 5.8–6.2 (m, 1), 6.4–7.0 (m, 1), 6.31 (d, 6, J = 11), 8.44 (d, 3, J = 7), 8.71 (d, 3, J = 7)
5f	40[a] 99[b]	128–129.5	6.23 (d, 6, J = 11), 6.0–7.3 (m, 3), 6.9 (broad, 1, NH), 9.00 (s, 9)
5g	Low[a] 99[b]	58–61	6.27 (d, 3, J = 11), 6.28 (d, 3, J = 11), 6.5–7.3 (m, 2, 1 H exchanges with D_2O), 8.35 (s, 3), 8.45 (s, 3), 8.70 (d, 3, J = 7)
5h	99	71–73	5.0–5.6 (broad, 1, NH), 6.35 (d, 6, J = 11), 4.53 (s, 2), 8.70 (s, 6)
5i			4.8–5.4 (broad, 1, NH), 6.35 (d, 6, J = 11), 6.94 (dd, 2, J = 7, 9, collapses into a doublet, J = 9, upon exchange of NH with D_2O), 8.43 (s, 6)

[a] By Cl_2 addition to **3** followed by $NaHSO_3$ reduction. [b] By HCl addition to **3**.

in C and H) analyses. The following aziridines have not previously been reported and are recorded here. The NMR spectra below were taken on a Varian A-60A spectrometer in CCl_4 solution.

Dimethyl *N*-(*cis*-2-methyl-2-phenylaziridinyl)phosphonate (3c) was obtained from *threo*-1-azido-1-phenyl-2-iodopropane in 83% yield after two distillations: bp 124–128 °C (0.1 mm); NMR τ 2.59 (s, 5), 6.22 (d, 3, J = 11 Hz), 6.26 (d, 3, J = 11 Hz), 6.4 (buried, 1), 6.8–7.7 (m, 1), and 9.03 (dd, 3, J = 5.5, 1.5 Hz).

Dimethyl *N*-(2-*tert*-butylaziridinyl)phosphonate (3f) was obtained by adding trimethyl phosphite (50 g) in 50 ml of cyclohexane to 75.4 g of 1-azido-2-iodo-3,3-dimethylbutane in 150 ml of cyclohexane at such a rate that gentle distillation of the cyclohexane occurred. After 1 day at room temperature the reaction was complete. Removal of the solvent in vacuo followed by distillation through a short path distillation apparatus gave two major fractions, one boiling at about 70 °C and one at about 100 °C (0.1 mm). Redistillation of the lower boiling fraction through a 6-in. column packed with glass helices gave 43 g (68%) of **3f**, bp 69–72 °C (0.1 mm). Redistillation of the higher boiling fractions through a short path distillation apparatus gave 15.5 g (14%) of dimethyl *N*-methyl-*N*-(2-iodo-3,3-dimethyl-1-butyl)phosphoramidate, bp 108–112 °C (0.09 mm). The NMR of **3f** showed τ 6.29 (d, 6, J = 11 Hz), 7.5–8.4 (m, 3), and 9.08 (s, 9).

Dimethyl *N*-(2,2-dimethylaziridinyl)phosphonate (3h) was obtained from 2-azido-1-iodo-2-methylpropane in 95% yield: bp 56–62 °C (0.1 mm); NMR τ 6.27 (d, 6, J = 11 Hz), 7.91 (d, 2, J = 14 Hz), and 8.62 (d, 6, J = 0.6 Hz).

Dimethyl *N*-(2,2,3,3-tetramethylaziridinyl)phosphonate (3j) was obtained from 2-azido-3-iodo-2,3-dimethylbutane on a small scale in 50% yield: approximate bp 70 °C (0.1 mm); NMR τ 4.37 (d, 6, J = 11 Hz) and 8.63 (d, 12, J = 0.7 Hz).

Dimethyl *N*-(*trans*-2-methyl-3-*tert*-butylaziridinyl)phosphonate (3k) was obtained from *erythro*-4-azido-3-iodo-2,2-dimethylpentane in 84% yield: bp 68–70 °C (0.07 mm); NMR τ 6.28 (d, 3, J = 11 Hz), 6.30 (d, 3, J = 11 Hz), 7.3–8.2 (m, 2), 8.58 (dd, 3, J = 5, 0.54 Hz), and 9.10 (s, 9).

Dimethyl *N*-(*cis*-2-methyl-3-*tert*-butylaziridinyl)phosphonate (3l) was obtained as follows. IN_3 addition to *cis*-4,4-dimethyl-2-pentene according to a published[10] procedure gave *threo*-4-azido-3-iodo-2,2-dimethylpentane in 92% yield. An analytical sample was provided by bulb-to-bulb distillation at 85 °C (0.07 mm): NMR τ 6.08 (d, 1, J = 1.5 Hz), 6.78 (dq, 1, J = 1.5, 6 Hz), 8.60 (d, 3, J = 6 Hz), and 8.85 (s, 9). This material was converted to **3k** in 81% yield: bp 72–76 °C (0.1 mm); NMR τ 6.29 (d, 6, J = 11 Hz), 7.2–8.3 (m, 2), 8.76 (dd, 3, J = 6, 1.2 Hz), and 9.0 (s, 9).

General Procedure for Chlorine Ring Opening of Aziridinylphosphonates 3. The aziridines **3** were mixed with a 5–12% solution of chlorine in CCl_4 calculated to contain a 10–20% excess of chlorine. The reaction was allowed to proceed at 5 °C until complete (NMR monitoring). Removal of the remaining chlorine and solvent in vacuo gave the phosphoramidates **4** in the yield indicated in Table I. Generally the product thus obtained was fairly pure (NMR); however, those aziridines requiring long contact times (**3c, 3f,** and **3g**) contained up to about 25% impurities.

Table II. Long-Range P–H Coupling in *N*-Aziridinyl Phosphonates 3

Compd	Chemical shift[a]	J_{CH_3-P} Hz
3b	154.7	0
3c	94.0	1.3
3d	131.0	0
3e	118.2	1.4
3g	120.3	1.2
	120.8	
	140.3	
3h	136.1	0.70
3j, $R_1 = R_2 = R_3 = R_4 = CH_3$	134.0	0.70
3k, $R_1 = CH_3$; $R_4 = C(CH_3)_3$; $R_2 = R_3 = H$	138.9	0.65
3l, $R_1 = CH_3$; $R_3 = C(CH_3)_3$; $R_2 = R_4 = H$	135.0	1.2
3m, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$	128.0	1.15

[a] At 100 MHz.

General Procedure for $NaHSO_3$ Reduction of *N*-Chlorophosphoramidates (4). A mixture of 5 g each of **4** and $NaHSO_3$ was stirred together in 50 ml of methanol (water bath cooling). The methanol was removed in vacuo and the residue extracted with 300 ml of ether. After drying ($MgSO_4$) the ether was removed in vacuo and the residue recrystallized (−30 °C) giving pure product. Repeated recrystallization gave the analytical samples of **5** with the melting points indicated in Table I.

General Procedure for HCl Ring Opening of Aziridinylphosphonates (3). To a 10% solution of **3** in ether in a dry ice–acetone bath was added a 5% solution of anhydrous HCl in ether calculated to contain 5% excess HCl. After the solution was warmed to room temperature the ether was removed in vacuo to give the crude product. In this way **5e** (99% crude yield, crude mp 81–84 °C), **5g** (99% crude yield, crude mp 44–50 °C), **5a** (69% yield of recrystallized product, mp 58–63 °C), and **5f** (99% crude yield, crude mp 128–129 °C) were synthesized. **3h** gave a 46:54 mixture of **5h** and **5i** by NMR analysis.

Determination of the Relative Chlorination Rates of 3a, 3b, and 3c. In a NMR tube at 0 °C were mixed 0.5 ml each of a 0.10 M

solution of Cl_2 and a 0.10 M solution of **3a, 3b,** or **3c** in CCl_4. The tube was placed in the probe of a Varian A-60A spectrometer held at 2 °C. The relative intensities of the aromatic protons vs. the benzylic protons in the products were compared by integration. Under these conditions the time required for 40% reaction was 3, 55, and 1440 min for **3a, 3b,** and **3c,** respectively. This gives a relative rate of chlorination of 460:17:1.

***N*-Azetidinyltriphenylphosphonium iodide (10)** was prepared in several steps from acrolein as follows. A solution of β-azidopropionaldehyde (prepared from 17.2 g of acrolein)[11] in ether was added with ice bath cooling to a stirred solution of 5 g of $NaBH_4$ in 30 ml of H_2O at such a rate that the temperature remained below 20 °C. After 10 min the aqueous phase was saturated with NaCl and the ether separated, dried ($MgSO_4$), and removed in vacuo giving 17.5 g (65% based on acrolein) of 3-azido-1-propanol. This product was added dropwise to 12 g of $SOCl_2$ in 15 ml of pentane. Removal of the solvent and distillation gave 9.25 g (58%) of 1-azido-3-chloropropane: bp 51 °C (15 mm); NMR τ 6.2–6.7 (overlapping triplets, 4, J = 7 Hz) and 8.0 (quintet, 4, J = 7 Hz). Treatment of 23.8 g of this material with 60 g of NaI in 500 ml of 2-butanone at reflux for 15 h gave, after water–pentane workup, 33 g (78%) of 1-azido-3-iodopropane: bp 83–84 °C (15 mm); NMR τ 6.7 (overlapping triplets, J = 7 Hz) and 8.0 (m, 2). When 5.4 g of this material was refluxed with 6.55 g of triphenylphosphine in 150 ml of hexane for 3 h, after cooling and filtration 5.4 g (49%) of **10** was obtained, mp 157–161 °C. The analytical sample was obtained by recrystallization from absolute ethanol/2-propanol and had mp 162–165 °C after drying at 65 °C (20 mm); NMR τ 2.0–2.5 (m, 15), 5.7 (m, 4, J_{P-H} = 4.0, J_{H-H} = 7.5 Hz), and 6.8–7.6 (m, 2, J_{PNCCH} = 4.5, J_{H-H} = 7.5 Hz).

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Registry No.—**3a,** 27356-57-6; **3b,** 27278-93-9; **3c,** 58503-29-0; **3d,** 30271-50-2; **3e,** 27278-92-8; **3f,** 58503-30-3; **3g,** 27356-56-5; **3h,** 58503-31-4; **3j,** 58503-32-5; **3k,** 58503-33-6; **3l,** 58503-34-7; **3m,** 58503-35-8; **4a,** 58503-36-9; **4b,** 58503-37-0; **4c,** 58503-38-1; **4d,** 58503-39-2; **4e,** 58503-40-5; **4f,** 58503-41-6; **4g,** 58503-42-7; **4h,** 58503-43-8; **4i,** 58503-44-9; **5a,** 58503-45-0; **5b,** 58503-46-1; **5d,** 58503-47-2; **5e,** 58503-48-3; **5f,** 58503-49-4; **5g,** 58503-50-7; **5h,** 58503-51-8; **5i,** 58503-52-9; **10,** 58503-53-0; **10** pentavalent form, 58503-54-1; *threo*-1-azido-1-phenyl-2-iodopropone, 58503-55-2; trimethyl phosphite, 121-45-9; 1-azido-2-iodo-3,3-dimethylbutane, 58503-56-3; 2-azido-1-iodo-2-methylpropane, 58503-57-4; 2-azido-3-iodo-2,3-dimethylbutane, 58503-58-5; *erythro*-4-azido-3-iodo-2,2-dimethylpentane, 16717-75-2; *cis*-4,4-dimethyl-2-pentene, 26232-98-4; *threo*-4-azido-3-iodo-2,2-dimethylpentane, 58503-59-6; β-azidopropionaldehyde, 58503-60-9; 1-azido-3-chloropropane, 58503-61-0; 1-azido-3-iodopropane, 58503-62-1.

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Synthesis of 3-Hydroxy-, 3-Chloro-, and 3-Methoxy-3-cephems from Penicillins via 4-Dithio-2-azetidinone Intermediates[1]

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Cyclization of monocyclic dithioazetidinone **2** to 3-methylene cepham **3** with potassium iodide was accomplished. A key intermediate **3** after ozonolysis afforded 3-hydroxy-3-cephem **5,** which in turn was treated with phosphorus trichloride in dimethylformamide to give 3-chloro-3-cephem **6.** From the reaction of the enol **5** with diazomethane the corresponding 3-methoxy-3-cephem **7** was obtained. Preparation of compounds **3, 5, 6,** and **7** from **2** and **4** is significant since it represents the first synthesis of directly 3-substituted cephalosporins from penicillins.

Recently a new series of potent cephalosporin antibiotics having halo and methoxy groups attached directly to the 3 position of the 3-cephem ring system have been discovered.[2] These antibiotics were synthesized from various cephalosporanic acids, in which the 3-acetoxymethyl group was converted to 3-methylene cephams.[3] The latter compounds were ozonized to the 3-hydroxy-3-cephems and converted to 3-methoxy- and 3-chloro-3-cephems by standard methods. While this synthetic scheme led directly to 3-substituted cephalosporins, there still existed a need to prepare these antibiotics more economically from penicillins. For this reason we sought a shorter synthesis from readily available penicillins.

It seemed to us that a key intermediate, 3-methylene cepham **3,** might be synthesized from a monocyclic azetidinone **2.** The desired 4-benzothiazol-2′-yldithio-2-azetidinone (**2**) was prepared from 2β-chloromethylpenam 1-(*R*)-sulfoxide (**1**) by refluxing with 2-mercaptobenzothiazole in benzene for 30–50 min according to the method described by Kamiya and co-workers.[4] The first transformations attempted on compound **2** centered at the allylic halide position. However, **2** did not react with silver nitrate in acetone at room temperature even after prolonged refluxing (24 h) with an excess of silver salt. Nucleophilic displacement of the allylic chloride in **2** with sodium thiocyanate in refluxing acetone for 20 h also did not succeed. This was surprising since we had expected the allyl halide to be very reactive. Our attention was then turned to reduction of the disulfide linkage in **2.** We believed that reduction should give an intermediate having a mercapto group, and hopefully after nucleophilic displacement as depicted by A, the desired 3-methylene cepham **3** would be formed. However, reduction with (a) stannous chloride in THF, (b) sodium cyanoborohydride in methanol/dimethylformamide