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Chemical Transformations of Penicillins and Cephalosporins. Mechanism and Stereochemistry of the Interconversions of Penam and Cepham Systems[1]

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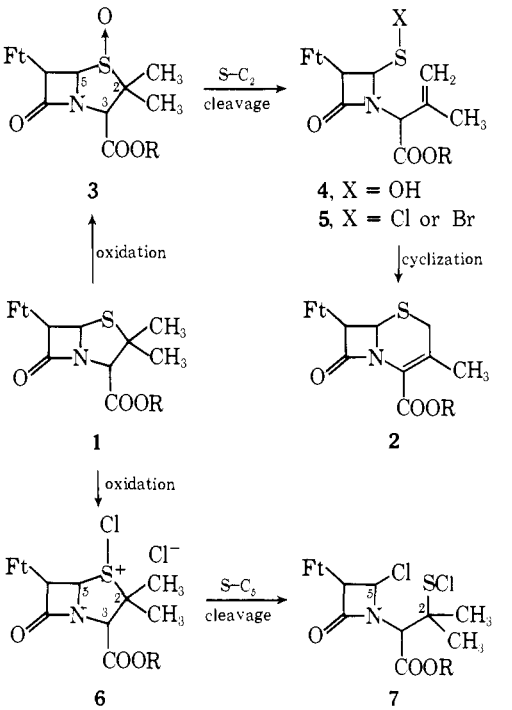
Abstract: Isomeric penam and cepham compounds have been prepared and isolated. It has been established that a thiiranium ion is a common intermediate in the interconversions of penam and cepham systems. The mechanism and stereochemistry of these interconversions have been studied in detail. A new synthesis of deacetoxycephalosporin starting from substituted penams and cephams is reported.

In the last decade the chemical modifications of azetidinone antibiotics (penicillins and cephalosporins) have been studied very actively. Since cephalosporins have been shown to be very effective antibiotics, the conversion of penicillins **1** to cephalosporins **2** has received considerable attention.[2] The difference between these two classes of compounds is in the nature of a heterocyclic ring attached to the four-membered azetidinone. In order to make **2** from **1,** an oxidative enlargement of the thiazolidine system in **1** has to be performed. Such a ring expansion has been realized by the following sequence of reactions, i.e., (a) oxidation of sulfur, (b) the cleavage of the $S-C_2$ bond, and (c) the cyclization to a six-membered dihydrothiazine. In this process the intermediate sulfenic acid **4** is formed, as was first suggested by Morin et al.[3] and later confirmed by Cooper and Barton et al.[4]

During studies of the electrophilic opening of the thiazolidine ring in penicillins, we have carried out a similar set of reactions (oxidation and the cleavage of an S-C bond).[5] However, in contrast to the $S-C_2$ bond cleavage reported in the formation of **4,** we observed the cleavage of an $S-C_5$ bond and formation of the sulfenyl chloride (**7**). Thus, oxidation of penicillin **1** with chlorine affords a chlorosulfonium chloride intermediate **6** which rearranges to the more stable sulfenyl chloride **7.** Since compounds having the sulfenyl halide group attached directly to the azetidinone ring, such as in **5,** are attractive intermediates for synthesis of deacetoxycephalosporins, other possibilities for making compounds of type **5** were explored.

A logical approach for the preparation of **5** would be to generate **4** by thermolysis of sulfoxide **3** and subsequently convert it to **5** by standard methods for the preparation of acid halides. Indeed, treatment of penicillin sulfoxide **3** (R = CH_3) with thionyl chloride and triethylamine in boiling carbon tetrachloride gives the highly reactive intermediate **5** which immediately cyclizes to isomeric penams **8** and **9** in the ratio of ca. 3:4.[6] Similarly, treatment of the sulfenic acid **4** (R = *p*-NB) with phosphorus tribromide in dichloromethane at room temperature gave **10** and **11** in the ratio of ca. 1:1.

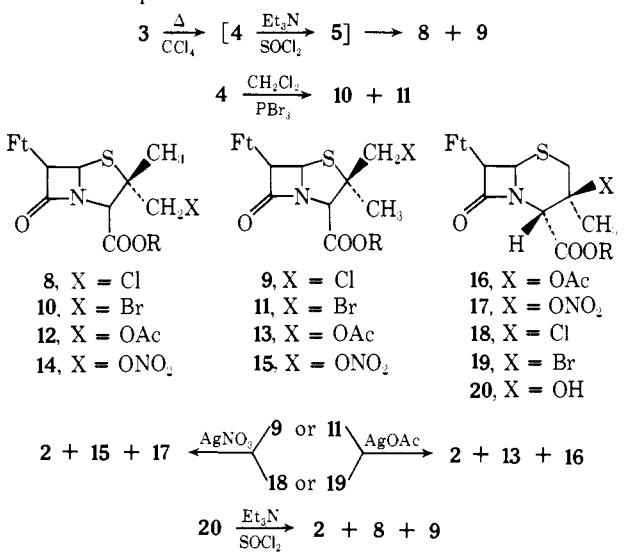


3 **4**, X = OH; **5**, X = Cl or Br; **1** **2** **6** **7**

a, R = CH_3; b, R = $CH_2C_6H_4$-*p*-NO_2 (*p*-NB);
c. R = $CH_2C_6H_4$-*p*-OCH_3 (*p*-MB); Ft = phthalimido

The structure and the stereochemistry of these isomers could not be established unequivocally on the basis of ir, NMR, and mass spectra alone. At the outset of our studies, we had some difficulties in distinguishing the isomeric 2-halomethylpenam and 3-halocepham derivatives, because the ir, NMR, and mass spectra are not discernible and especially since the AB quartet signals for methylene protons in the NMR spectra are nondistinctive. Chemical evidence was, therefore, required to substantiate the configuration and conformation of these isomeric products. Since Spry[7] has described 2-acetoxymethylpenam sulfoxides, it seemed

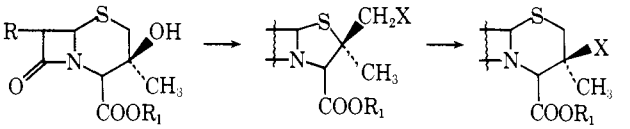
that a conversion of the isomeric halomethylpenams to the acetoxy derivatives should be a simple way to confirm the structure of these compounds. For that reason 2α-chloromethylpenam **8** (R = CH_3) was treated with silver acetate in acetic acid and the acetate **12a** was obtained in almost quantitative yield and subsequently oxidized to the corresponding sulfoxide. Comparison of the spectral data of the product so obtained with the sulfoxide of **12a** described by Spry[7] confirmed the structure and the stereochemistry of α-isomer **8a.** However, when 2β-methyl substituted penam **9** (R = CH_3) was treated with silver acetate in acetic acid for 5 min, the mixture of three compounds, i.e., **2a, 13a,** and **16a,** was obtained in the ratio 1:3:3. In addition, it was also found that cepham **18** (R = CH_3) upon treatment with silver acetate in acetic acid for 5 min gave the same mixture of **2a, 13a,** and **16a** in approximately the same ratio (1:3:3) as 2β-chloromethylpenam isomer **9a.** Similarly, when 2β-methyl substituted penams **9** and **11** or 3β-halocephams **18** and **19** (R = CH_3 and *p*-NB) were treated with silver nitrate in acetone, a mixture of **2, 15,** and **17** in the ratio of ca. 1:5:15 was obtained. However, the reaction of the α-isomer **8** (R = CH_3) with silver nitrate afforded, surprisingly, only one product, i.e., 2α-nitrooxymethylpenam (**14a**). While the reactions of 2α-halomethylpenams with silver salts were useful in confirming the configuration of α-isomers, the similar reactions with β-isomers did not help us in solving the structure and stereochemistry of β-isomeric penams and cephams.[8,9] Finally, the structural problems were solved by NMR and C-13 nuclear magnetic resonance[10,11] and X-ray crystallography as well as by comparison with authentic samples.[12]



a, R = CH_3; b, R = $CH_2C_6H_4$-*p*-NO_2 (*p*-NB);
c, R = $CH_2C_6H_4$-*p*-OCH_3 (*p*-MB); Ft = phthalimido

Initially, we assigned the cepham structure **18** to the penam derivative **9** (R = CH_3) on the basis of spectral data, chemical reactions, and mechanistic considerations.[9] Since our preliminary report, however, we have found that **9** (R = CH_3 or *p*-NB), during the purification by chromatography over silica gel or simply by keeping in a flask at room temperature for a week or two, rearranges to the isomeric cepham **18** (R = CH_3 or *p*-NB).

These conversions, together with skeletal rearrangement of **9** to **16, 17,** and **18,** represent a new conversion of methyl-substituted penicillins to 3-substituted cephams.[13] This type of conversion is much faster with compounds having better leaving groups such as the nitroxy or bromo substituents in **15** and **11.** Thus, **11** or **15** (R = CH_3 or *p*-NB) in the solid state rearranges at room temperature over a 2- to 3-day period to the corresponding cephams **17** or **19.** The rearrangement proceeds also in a solution and by heating. Similar results were recently reported by Kamiya and coworkers.[14] Conversion of cephams **18** and **19** to **13** and **15** is illustrative of the ring contraction of a cepham system to a penam system[15,16a] and this is, in fact, the first conversion of a cepham to a penam.[16b]



21 **22** **23**

R = $PhOCH_2CONH$; R_1 = $CH_2C_6H_4$-*p*-NO_2

The ring contraction of 3β-hydroxycepham (**20**) (R = CH_3) with thionyl chloride in the presence of triethylamine was reported earlier.[6] The same reaction was repeated with *p*-nitrobenzyl and *p*-methoxybenzyl ester of **20** and the corresponding esters of **2, 8,** and **9** were obtained. On the basis of the NMR spectrum, the ratio of components was estimated to be ca. 1:2:10, respectively. The major component **9** in the case or *p*-NB of *p*-MB ester was isolated in 57–60% yield by recrystallization and from the filtrate **2** and **8** were isolated by chromatography.

In order to determine whether the ring contraction of 3β-hydroxycephams is limited only to cephams having the phthalimido side chain, *p*-nitrobenzyl ester of phenoxyacetamido-3β-hydroxycepham (**21**) was refluxed with thionyl chloride in the presence of triethylamine. Only starting material was recovered. However, when **21** was refluxed with thionyl chloride and dimethylformamide in boiling benzene for 30 min, the corresponding 2β-chloromethylpenam (**22**) (X = Cl) was obtained. After keeping **22** in a flask at room temperature, it rearranged completely to 3β-chlorocepham (**23**). The conversion of 3-hydroxycephams **20** (R = CH_3, *p*-NB, and *p*-MB) and **21** (R_1 = *p*-NB) to the corresponding esters of **8, 9,** and **22** are additional examples of the ring contraction of a cepham to a penam.

Since our ultimate objective was the new route for the synthesis of cephalosporins from economically available penicillins, the final part of our project was to study the conversion of 2-methyl-substituted penams and 3-substituted cephams into deacetoxycephalosporins. We have found that the ease of conversion of these derivatives to Δ^3-cephems **2** is dependent upon the properties of the leaving group. With good leaving groups such as Br and ONO_2, the elimination is substantially faster than with poorer leaving groups (such as Cl or OAc).[17] For example, compounds **11, 15, 17, 19, 22,** and **23** were converted to the corresponding deacetoxycephalosporin **2** by treatment with tertiary bases or simply by heating in different solvents. However, the esters of **9a** and **13a** could not be transformed to **2a** under these conditions. Transformation of substituted penicillins and cephams into Δ^3-cephems represents, in fact, a new synthesis of deacetoxycephalosporins from penicillins. The utilization of 2-substituted methylene penicillins in the synthesis of cephalosporins was first suggested by Stork and Cheung[18] and later elaborated by Wolfe.[19] Recently, this concept was also realized in an elegant work published by Kamiya and coworkers.[14]

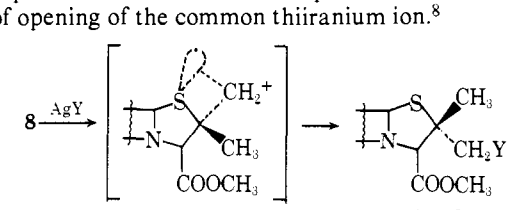
Mechanism and Discussion

Although the mechanism and stereochemistry of the ring expansion and ring contraction reactions were adequately explained by intermediacy of a common thiiranium ion E, there were still some questions as to why β-halomethylpenam isomers give three products in the reaction with silver

salts, while the corresponding α isomers yield only one compound. In addition the fact that two, three, or four products were obtained in the reaction of penicillin sulfoxides or 3β-hydroxycephams with halogenating agents also requires an adequate explanation. If the mechanism described in the preliminary communication[6] is correct, four products should be obtained in each reaction, i.e., 2α- and 2β-methyl-substituted penams (I and III) and 3α- and 3β-substituted cephams (II and IV). Formation of isomeric penams and cephams indicates that the episulfonium ion E exists in two configurations as pointed out previously by Cooper and Spry.[20] Stereoformulas A and B are illustrative of the fact that the bridging methylene group can be attached to the sulfur atom from the α or β face, thus resulting in the thiiranium ions A and B. Since the stereochemistry of the intermediate thiiranium ions is fixed, their reaction with nucleophiles will result in final products of predictable configurations. In the case of α-methylene bridging intermediate A, the opening of the thiiranium ion will give a product having a nucleophilic substituent attached from the α face. Similarly, the nucleophilic attack of an anion on the thiiranium intermediate B will result in 2β- and/or 3β-substituted derivatives III and IV.

Although the configuration of the products derived from a thiiranium intermediate of known stereochemistry can be predicted, the ratio and the number of the products formed, therefrom, depend on their thermodynamic stability and on the reaction conditions employed. Since the olefinic product **2** was always isolated, but not compound II, we believe that cepham II is thermodynamically unstable and easily transformed, via highly favorable trans elimination, to the more stable olefin **2**. We have found that stability of III is dependent upon the character of a substituent X. If X is good leaving group, e.g., Br or ONO_2 (as in **11** and **15**), III is easily transformed to IV or **2** depending upon reaction conditions. But, when X is OAc or Cl, penam derivative III is relatively more stable, and, therefore, two, three, or four products are formed in the reactions with chlorinating agents or acetic anhydride.[7]

The reactions with silver salts were performed under conditions likely to give kinetically controlled products. Since the α-isomer **8** with silver salts affords only one product, i.e. **12** or **14**, and the β-isomers **9** and **11** yield three compounds (**2, 13, 16,** or **2, 15, 17**), evidently these isomeric penam derivatives react differently under the same reaction conditions. In the case of β isomers, a silver ion abstracts halogen and the resultant carbonium ion (primary or tertiary) is stabilized by nucleophilic sulfur. Since the methyl group in the starting material is α, as chlorine is leaving and sulfur approaches the formed carbonium ion, the methylene bridging is forced to assume β stereochemistry resulting in only so-called β-thiiranium ion B. Consequently, the opening of the β form by an anion will give III and IV, which are partially transformed to olefin **2**. Hence only three products, with a substituent X being attached from the β face, were isolated in the reactions with silver salts. However, the formation of one product starting with the α-halomethyl isomer might be explained to proceed via two possible mechanisms: (i) participation of the ester group in the stabilization of the carbonium ion, or (ii) by "abnormal" type of SN1 substitution. In the first case there is a possibility that upon abstraction of halogen the formed carbonium ion is preferentially stabilized by ester group. Consequently, the intermediacy of episulfonium ion is minimized and, therefore, only one product is possible. In the case of an "abnormal" type of SN1 substitution, the steric repulsion between the bulky phthalimido and CH_3 groups makes the access of sulfur electrons too limited stereochemically to allow the formation of a strong bond and the unshared electrons combine only weakly, if at all, with the carbonium ionic center.[21,22] Therefore, the primary carbonium ion is loosely stabilized, short lived, and selectively attacked by the available nucleophile (AcO^- or O_2NO^-) resulting in the formation of only one product (**12** or **14**). Accordingly, we suggest that the major reason for the difference in the product formation is the degree and nature of stabilization of the primary carbonium ion by a neighboring group.[23] From the above discussion it is apparent that the product formation and stereochemical course of described reactions depend upon thermodynamic and kinetic factors. The cephems and cephams are the thermodynamic products while the isomeric penams are kinetic products of opening of the common thiiranium ion.[8]



12, Y = OAc
14, Y = ONO_2

Our results obtained during the study of the interconversions of penam and cepham systems have led us to believe that biosynthesis of penicillin N,[24] deacetoxycephalosporin C,[25] and closely related substances is likely explained as proceeding via a common thiiranium ion E (R_a = α-aminoadipic acid; R = H). The formation of the final products most likely depends upon conditions in fermentation pro-

deacetoxycephalosporin C ⟵ E ⟶ penicillin N

cesses. Although at present there seems to be no experimental biosynthetic evidence supporting this hypothesis, we hope that a systematic search for a common denominator E could result in the discovery of new azetidinone antibiotics.

Experimental Section[26]

Reaction of Methyl 6β-Phthalimidopenicillanate 1-Oxide (3a) with Thionyl Chloride. Preparation of 8a and 9a. A solution of 2.25 g (6 mmol) of methyl 6-phthalimidopenicillanate 1-oxide and 0.47 ml (6.5 mmol) of purified and distilled thionyl chloride in 70 ml of dry carbon tetrachloride was heated to reflux and 0.84 ml (6 mmol) of triethylamine in 20 ml of dry carbon tetrachloride was added dropwise over 1 hr. The reaction mixture was then cooled and washed with water and brine and dried ($MgSO_4$). Evaporation in vacuo gave a light yellow foam. Chromatography on 70 g of acid washed silica gel yielded three fractions, the first of which contained 0.78 g (33%) of methyl 6β-phthalimido-2β-chloromethyl-2α-methylpenam-3α-carboxylate (**9a**). Recrystallization from diethyl ether gave colorless needles: mp 107–112°; $[\alpha]^{27}D$ +265.6° (CH_3CN); ir ($CHCl_3$) 1802, 1732, 1785, and 1748 cm^{-1}; *m/e* 394, 366, 358, 307, 271.

The second fraction (0.21 g) contained a 3:1 mixture (by NMR) of the 2β-chloromethylpenam methyl ester (**9a**) and the isomeric 2α-chloromethylpenam methyl ester (**8a**). The latter was obtained from the third fraction as a white foam (0.25 g, 11%) which was recrystallized from diethyl ether to give colorless needles of **8a:** mp 166–167°; $[\alpha]^{27}D$ −221.0° (CH_3CN); ir ($CHCl_3$) 1803, 1786, 1745, and 1737 cm^{-1}; *m/e* 394, 366, 358, 307, 280, 271.

Reaction of Methyl 7β-Phthalimido-3β-hydroxy-3-methylcepham-4-carboxylate (20a) with Thionyl Chloride. To a refluxing solution of 3.76 g (10 mmol) of methyl 7-phthalimido-3β-hydroxy-3-methylcepham-4-carboxylate and 1.3 ml (18 mmol) of thionyl chloride in 180 ml of dry carbon tetrachloride, 1.6 ml (11 mmol) of triethylamine in 20 ml of dry carbon tetrachloride was added dropwise during 45 min. After addition of the triethylamine was completed, the mixture was refluxed for an additional 0.5 hour. The solution was then filtered and evaporated in vacuo to dryness. The crude product was taken up in 80 ml of ethyl acetate and washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave a light yellow amorphous solid which was triturated with 50 ml of a mixture of diethyl ether–ethyl acetate (1:1). After filtering and washing with diethyl ether, 1.72 g of a white amorphous solid of methyl 6β-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (**9a**) was obtained. It was recrystallized from diethyl ether to give thin colorless needles, mp 107–112°. This product was identical (NMR and ir) with a sample of **9a** prepared from a sulfoxide and thionyl chloride.

The filtrate was chromatographed (silica, 95:5, benzene–ethyl acetate) and an additional 740 mg of **9a** was collected; total yield, 62%. Subsequent fractions contained a mixture of **2a** and **8a** which was separated by repeated chromatography.

Reaction of *p*-Nitrobenzyl 3β-Hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (20b) with Thionyl Chloride. Triethylamine (1.2 ml, 9.8 mmol) in 20 ml of dry 1,2-dichloroethane was added dropwise to a refluxing solution of *p*-nitrobenzyl 3β-hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (3.98 g, 8 mmol) and thionyl chloride (0.7 ml, 9 mmol) in 250 ml of dry 1,2-dichloroethane. After 1 hr at reflux another 0.5 ml of thionyl chloride and 0.5 ml of triethylamine was added to the reaction mixture. After 2 more hr at reflux the mixture was cooled and evaporated in vacuo to dryness. The crude product was taken up in 80 ml of chloroform, refluxed with 7 g of decolorizing carbon (Darko G-60), and filtered. The filtrate was washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo to dryness. Recrystallization from ethyl acetate–diethyl ether–petroleum ether gave 2.3 g (56%) of *p*-nitrobenzyl 2β-chloromethyl-2α-methyl-6β-phthalimidopenam-3α-carboxylate (**9b**) as tan needles: mp 161–163°; ir ($CHCl_3$) 1809, 1787, 1743, and 1735 cm^{-1}.

The mother liquor contained *p*-nitrobenzyl 2α-chloromethyl-2β-methyl-6β-phthalimidopenam-3α-carboxylate (**8b**) and *p*-nitrobenzyl 7β-phthalimido-3-cephem-4-carboxylate (**2b**). The separation of this mixture (900 mg) by HPLC (silica gel, toluene–ethyl acetate, 9:1) resulted in isolation of 270 mg of 2α-chloromethylpenam **8b,** which was recrystallized from a mixture of ether and cyclohexane.

Rearrangement of *p*-Methoxybenzyl 3β-Hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (20c) with Thionyl Chloride. To a refluxing solution of 7.23 g (15 mmol) of *p*-methoxybenzyl 3β-hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate and 1.30 ml (16 mmol) of thionyl chloride in 400 ml of 1,2-dichloroethane was added 2.10 ml (15 mmol) of triethylamine in 50 ml of 1,2-dichloroethane dropwise. After 90 min at reflux another 0.3 ml of thionyl chloride and 0.2 ml of triethylamine were added to the reaction mixture. The mixture was then refluxed for an additional 30 min, cooled, and evaporated to dryness. The crude product was chromatographed on an acid-washed silica gel column (250 g, 4 × 35 cm) developed with ethyl acetate–benzene (6:94) solution. A total of 4.5 g (60%) of *p*-methoxybenzyl 2β-chloromethyl-2α-methyl-6β-phthalimidopenam-3α-carboxylate (**9c**) was obtained: ir ($CHCl_3$) 1806, 1788, 1745, and 1736 cm^{-1}; *m/e* 500, 472, 464, 343.

Subsequent fractions contained 0.8 g of 2α-chloromethyl isomer **8c** and 3-cephem **2c.**

Preparation of Methyl 7β-Phthalimido-3β-hydroxy-3α-methylcepham-4-carboxylate (20a).[17] Methyl 6β-phthalimidopenicillin-3-carboxylate 1-oxide (20.0 g, 53.2 mmol) was added to a refluxing mixture of 100 ml of benzene and 2 drops of sulfuric acid which had been dried azeotropically for 30 min with a Dean-Stark trap. The resulting mixture was refluxed for 2.75 hr and allowed to cool. The precipitate which formed was collected by filtration and the filtrate was evaporated to dryness for further recrystallization from benzene; total yield, 15 g (75%). A sample was also recrystallized from methylene chloride–cyclohexane, mp 195–196°, and was identical with the sample prepared earlier by Spry.

***p*-Nitrobenzyl 3β-Hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (20b).**[17] A mixture of 80 ml of benzene, 60 ml of *N,N*-dimethylacetamide, and 4 drops of H_2SO_4 was dried azeotropically for 30 min and then 15 g (30 mmol) of *p*-nitrobenzyl 6β-phthalimidopenicillinate 1-oxide was added. The mixture was refluxed for 30 min and the crude product was evaporated to dryness, slurried with 50 ml of ethyl acetate, and filtered. The desired product was obtained as a white powder (10.0 g, 33%). Recrystallization from chloroform–cyclohexane gave tan needles: mp 250–251°; ir (mull) 1790, 1782, 1743, and 1728 cm^{-1}.

Preparation of *p*-Methoxybenzyl 3β-Hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (20c).[17] A mixture of 4 drops of concentrated sulfuric acid in 60 ml of *N,N*-dimethylacetamide and 80 ml of benzene was dried azeotropically for 30 min with a Dean-Stark trap. After that, 5.0 g (10 mmol) of *p*-methoxybenzyl 6β-phthalimidopenicillanate 1-oxide was added and the mixture was refluxed for 30 min, cooled, and evaporated to near dryness. Ethyl acetate (150 ml) was then added and the resulting solution was evaporated in vacuo to dryness. The residue was then slurried with 50 ml of ethyl acetate and filtered to give 3.1 g (62%) of *p*-methoxybenzyl 3β-hydroxy-3α-methyl-7β-phthalimidocepham-4α-carboxylate (**20c**) as colorless crystals: mp 216–217°; ir (mull) 3460, 1802, 1781, 1739, and 1725 cm^{-1}.

Preparation of 2α- and 2β-Bromomethylpenams 10b and 11b from the Sulfenic Acid 4b. A solution of 0.23 ml of phosphorus tribromide in 40 ml of methylene chloride was cooled in an ice bath and 1.0 g (2 mmol) of the *p*-nitrobenzyl ester sulfenic acid **4b**[27] was slowly added. After stirring at room temperature for 15 min, the mixture was heated to reflux for 1 min, cooled, washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give a colorless foam. The NMR spectrum showed a mixture of **10b** and **11b** in the ratio of ca. 1:1. The mixture was separated by HPLC (silica gel, toluene–ethyl acetate, 9:1) giving 390 mg (35%) of **11b** and 360 mg (32%) of **10b.**

Reaction of Methyl 2α-Chloromethyl-2β-methyl-6β-phthalimidopenam-3α-carboxylate (8a) with Silver Acetate. Methyl 2α-chloromethyl-2β-methyl-6β-phthalimidopenam-3α-carboxylate (25 mg, 0.063 mmol) and 12 mg (0.07 mmol) of silver acetate were dissolved in 5 ml of acetic acid and heated on a steam bath for 5 min. Solvent was then evaporated in vacuo to dryness. The residue was taken up in 5 ml of chloroform and again evaporated to dryness. The NMR spectrum of the product so obtained agrees with that for methyl 2α-acetoxymethyl-2β-methyl-6β-phthalimidopenicillin-3α-carboxylate (**12a**) prepared by Spry.[7]

Reaction of Methyl 2α-Chloromethyl-2β-methyl-6β-phthalimid-

openam-3α-carboxylate (8a) with Silver Nitrate. To a solution of 268 mg (0.68 mmol) of methyl 2α-chloromethyl-2β-methyl-6β-phthalimidopenam-3α-carboxylate in 25 ml of acetone was added 161 mg (0.95 mmol) of silver nitrate. The resulting mixture was stirred at room temperature for 1.5 hr. The mixture was then evaporated in vacuo to dryness. The residue was taken up in 20 ml of chloroform, filtered, and again evaporated to dryness giving a yellow foam. Recrystallization from ethyl acetate–diethyl ether gave colorless needles of **14a:** mp 153.5–155°; *m/e* (M^+) 421, 394, 358, 319.

Reaction of Methyl 6-Phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (9a) with Silver Acetate. To a solution of 2.35 g (6 mmol) of methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (**9a**) in 75 ml of glacial acetic acid was added 1.10 g (6.6 mmol) of silver acetate. The reaction mixture was heated on a steam bath for 15 min and then filtered to remove the silver chloride precipitate. The filtrate was evaporated in vacuo to near dryness and the residue was taken up in 80 ml of ethyl acetate and washed with saturated $NaHCO_3$ solution, water, and brine. After drying ($MgSO_4$), the ethyl acetate solution was evaporated in vacuo to a white foam. A TLC (4:1, benzene–ethyl acetate) indicated a mixture of three products. Integration of the NMR showed a 3:3:1 mixture of methyl 7-phthalimido-3β-acetoxy-3-methylcepham-4-carboxylate (**16a**), methyl 6-phthalimido-2β-acetoxymethyl-2α-methylpenam-3-carboxylate (**13a**), and methyl 7-phthalimidodesacetoxycephalosporinate (**2a**), respectively. Chromatography on silica gel (5:95, ethyl acetate–benzene) gave 880 mg of the β-acetoxymethylpenam **13a.**

A second fraction contained 1.02 g of a 4:3 (by NMR) mixture of methyl 6-phthalimido-2β-acetoxymethylpenam-3-carboxylate (**13a**) and methyl 7-phthalimido-3β-acetoxy-3-methylcepham-4-carboxylate (**16a**), respectively. The structure of the latter was confirmed by comparison of the NMR with that of the authentic compound prepared by treatment of methyl 7-phthalimido-3β-hydroxy-3-methylcepham methyl ester with fluorosulfonic acid in acetic acid.

Methyl 7-Phthalimido-3β-acetoxy-3-methylcepham-4-carboxylate (16a). Fluorosulfonic acid (0.9 ml, 15 mmol) was added to a solution of methyl 7-phthalimido-3β-hydroxy-3-methylcepham-4-carboxylate (**20a**) (1.51 g, 4 mmol) in 70 ml of acetic acid at room temperature. The mixture was heated on a steam bath for 5 min, cooled, and evaporated in vacuo to near dryness. The resulting colorless syrup was taken up in 50 ml of ethyl acetate and slurried with 30 ml of saturated sodium bicarbonate solution. The organic layer was separated and washed successively with saturated $NaHCO_3$ solution, water, and brine. After drying the ethyl acetate solution was evaporated in vacuo to give a colorless foam. Recrystallization from ethyl acetate–cyclohexane gave 1.10 g (63%) of white crystalline methyl 7-phthalimido-3β-acetoxy-3-methylcepham-4-carboxylate (**16a**), mp 146–148°.

Reaction of Methyl 6β-Phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (9a) with Silver Nitrate. A solution of silver nitrate (0.85 g, 5 mmol) and methyl 6-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (**9a**) (1.17 g, 3 mmol) in 80 ml of acetone was refluxed for 20 min, cooled, and filtered. The filtrate was evaporated in vacuo to dryness. An NMR spectrum of the crude product showed ca. a 15:5:1 mixture of methyl 7-phthalimido-3β-nitrooxy-3-methylcepham-4-carboxylate (**17a**), methyl 6-phthalimido-2β-nitrooxymethylpenicillinate (**15a**), and methyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate, respectively. Chromatography of the product mixture on silica gel gave methyl 6-phthalimido-2β-nitrooxymethylpenicillinate (260 mg, 20% yield) which crystallized from chloroform to give colorless prisms: mp 115.5–117.5°; mass spectrum (M^+ 421, 394, 358, 319).

A second fraction (680 mg, 52%) was shown by NMR to be ca. an 8:1 mixture of methyl 7-phthalimido-3β-nitrooxy-3-methylcepham-4-carboxylate and methyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate (**2a**), respectively.

Reaction of *p*-Nitrobenzyl 6β-Phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (9b) with Silver Nitrate. A solution of *p*-nitrobenzyl 6β-phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (**9b**) (2.06 g, 4 mmol) and silver nitrate (1.0 g, 6 mmol) in 150 ml of acetone was refluxed for 0.5 hr, cooled, and evaporated in vacuo to dryness. The product was taken up in 250 ml of chloroform, heated to reflux, and filtered. The filtrate was evaporated in vacuo to dryness. An NMR spectrum of the crude mixture showed three products: *p*-nitrobenzyl 7-phthalimido-3β-nitrooxy-3-methylcepham-4-carboxylate (**17b**), *p*-nitrobenzyl 6-phthalimido-2β-nitrooxymethylpenicillinate (**15b**), and *p*-nitrobenzyl 7-phthalimidodesacetoxycephalosporinate (**2b**) in a ratio of ca. 13:3:1, respectively.

Reaction of *p*-Methoxybenzyl 6-Phthalimido-2β-chloromethyl-2α-methylpenam-3-carboxylate (9c) with Silver Nitrate. A solution of *p*-methoxybenzyl 6-phthalimido-2β-chloromethyl-2α-methylphenam-3-carboxylate (**9c**) (2.50 g, 5 mmol) and silver nitrate (1.2 g, 7 mmol, powdered) in 130 ml of acetone was refluxed on a steam bath for 30 min, cooled, and evaporated to dryness. Chloroform (100 ml) was added to the product, heated to near reflux, and AgCl filtered, and the filtrate was evaporated in vacuo to dryness. An NMR of the resulting colorless foam indicated a 20:6:1 ratio of *p*-methoxybenzyl 7-phthalimido-3β-nitrooxy-3-methylcepham-4-carboxylate (**17c**), *p*-methoxybenzyl 6-phthalimido-2β-nitrooxymethylpenicillinate (**15c**), and *p*-methoxybenzyl 7-phthalimidodesacetoxycephalosporin (**2c**), respectively. Chromatography on a 2.5 × 44 cm silica gel (80 g) column developed with 5% benzene–ethyl acetate gave 420 mg (16%) of *p*-methoxybenzyl 6-phthalimido-2β-nitrooxymethylpenicillinate (**15c**) as a white foam: ir ($CHCl_3$) 1651 (nitrate), 1736 (ester C=O), 1745 and 1788 (phthalimido C=O), and 1810 cm^{-1} (azetidinone C=O).

The next fractions contained 1.54 g of a 3:1 mixture of *p*-methoxybenzyl 7-phthalimido-3β-(nitrooxy)-3-methylcepham-4-carboxylate (**17c**) and *p*-methoxybenzyl 7-phthalimidodesacetoxycephalosporin (**2c**), respectively. Both products were identified by NMR spectroscopy and are separable by chromatography.

Reaction of *p*-Nitrobenzyl 2β-Bromomethyl-2α-methyl-6-phthalimidopenam-3-carboxylate (11b) with Silver Acetate. A mixture of 140 mg (0.25 mmol) of **11b**, 50 mg of silver acetate, and 5 ml of acetic acid was heated on a steam bath for 15 min. The precipitate was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 15 ml of ethyl acetate and washed with a saturated $NaHCO_3$ solution and brine. After drying, the solvent was evaporated and 110 mg of a colorless foam was obtained. A TLC plate showed three spots and the NMR spectrum indicated that **13b**, **16b**, and **2b** are formed in a ratio of ca. 8:9:1.

Reaction of *p*-Nitrobenzyl 2β-Bromomethyl-2α-methyl-6-phthalimidopenam-3-carboxylate (11b) with Silver Nitrate. A solution of 140 mg (0.25 mmol) of **11b** and 100 mg of silver nitrate in 20 ml of acetone was stirred at room temperature for 1 hr, and then evaporated to dryness. The residue was extracted with $CHCl_3$ and after the evaporation of a solvent, 126 mg (76%) of a colorless product was obtained. A TLC plate showed three spots and the NMR spectrum indicated that penam **15b,** cepham **17b**, and 3-cephem **2b** are present in a ratio of ca. 4:15:1.

Reaction of Methyl 3β-Chloro-3α-methyl-7-phthalimidocepham-4-carboxylate (18a) with Silver Acetate. Methyl 3β-chloro-3α-methyl-7-phthalimidocepham-4-carboxylate (50 mg, 12 mmol) (**18a**) and 22 mg (12 mmol) of silver acetate were dissolved in 10 ml of acetic acid and heated on a steam bath for 10 min. The solvent evaporated in vacuo, and the residue was then taken up in 15 ml of chloroform and again evaporated to dryness yielding a yellow foam. Quantitative NMR was used to determine the products to be methyl 7-phthalimido-3-cephem-4-carboxylate (**2a**), methyl 3β-acetoxy-3α-methyl-7β-phthalimidocepham-4-carboxylate (**16a**), and methyl 2β-acetoxymethyl-2α-methyl-6β-phthalimidopenam-4-carboxylate (**13a**) in a ratio of 1:2.8:3.1.

Reaction of Methyl 3β-Chloro-3α-methyl-7-phthalimidocepham-4-carboxylate (18a) with Silver Nitrate. A mixture of 0.10 g (0.25 mmol) of methyl 3β-chloro-3α-methyl-7-phthalimidocepham-4-carboxylate (**18a**) and 0.10 g (excess) of silver nitrate in 25 ml of acetone was refluxed for 35 hr (required for complete reaction), cooled to room temperature, evaporated in vacuo to dryness, slurried with 25 ml of chloroform, and filtered. The filtrate was again evaporated to dryness giving a white foam. NMR showed the products to be methyl 7β-phthalimido-3-cephem-4-carboxylate (**2a**), methyl 3β-nitrooxy-3α-methyl-7-phthalimidocepham-4-carboxylate (**17a**), and methyl 2β-nitrooxymethyl-2α-methyl-6-phthalimidopenam-3-carboxylate (**15a**) in a ratio of 2:15:1.

Reaction of 19b with Silver Acetate. A mixture of 112 mg (0.2 mmol) of **19b**, 45 mg of silver acetate, and 5 ml of acetic acid was heated on a steam bath for 15 min. The precipitate was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 15 ml of ethyl acetate and washed with a $NaHCO_3$ solu-

tion and brine. A colorless foam (83 mg, 72%) was obtained. The NMR spectrum indicated a mixture of **13b**, **16b**, and **2b** in a ratio of ca. 7:9:1.

Reaction of 19b with Silver Nitrate. A solution of 112 mg (0.2 mmol) of **19b** and 110 mg of silver nitrate in 20 ml of acetone was stirred at room temperature for 1 hr. After evaporation of the solvent, the residue was extracted with $CHCl_3$ and the solvent was evaporated again giving 77 mg (65%) of a colorless solid. The NMR spectrum of this product showed it to be a mixture of **15b**, **17b**, and **2b** in a ratio of 5:14:1.

Reaction of 22 with Silver Acetate. Silver acetate (200 mg) was added to a solution of *p*-nitrobenzyl 6-phenoxyacetamido-2α-methyl-2β-chloromethylpenam-3-carboxylate (**22**) (400 mg) in 10 ml of glacial acetic acid. The mixture was heated on a steam bath for 15 min, cooled, and evaporated in vacuo to near dryness. The crude product was taken up in 20 ml of ethyl acetate; the inorganic salts were filtered and the filtrate was evaporated to dryness. Comparative thin layer chromatography indicated three products, two of which had radiofrequency values corresponding to those of *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate and *p*-nitrobenzyl 7-phenoxyacetamido-3-acetoxy-3-methylcepham-4-carboxylate. Separation of the mixture by preparative thin layer chromatography gave the following: *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (58 mg, 17%); NMR ($CDCl_3$) 131 (s, 3, CH_3), 197 and 215 (AB q, J = 18 Hz), 275 (s, 2, side-chain CH_2), 302 (d, 1, J = 4.0 Hz), 322 (s, 2, ester CH_2), 353 (q, 1, J = 4.0 and 9.0 Hz), and 410–500 Hz (m, 9, ArH).

p-Nitrobenzyl 7-phenoxyacetamido-3-acetoxy-3-methylcepham-4-carboxylate (60 mg, 16%): NMR ($CDCl_3$) 92 (s, 3, 3-CH_3), 120 (s, 3, 3-OCOCH_3), 203 (s, 2, C_2H), 274 (s, 2, side-chain CH_2), 204 (s, 1, CH), 318 (s, 2, ester CH_2), 320 (d, 1, J = 4.0 Hz, azetidinone H), 340 (q, 1, J = 4.0 and 10.0 Hz), and 410–500 Hz (m, 9, ArH). This compound is identical with that prepared by methods of Gutowski et al.[17]

The other product is isolated as a mixture with *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate and is identified as *p*-nitrobenzyl 6-phenoxyacetamido-2-acetoxymethyl-2-methylpenam-3-carboxylate: NMR ($CDCl_3$), 85 (s, 3, C_2CH_3), 124 (s, 3, $OCOCH_3$), 228 and 260 (AB q, 2, J = 11.0 Hz), 274 (s, 2, side-chain CH_2), 285 (s, 1, C_3H), 320 (s, 2, ester CH_2), 342 (m, 2, azetidinone H), and 410–500 Hz (m, 9, ArH).

Rearrangement of 2β-Chloromethylpenam (9a) to 3β-Chlorocepham (18a) by Silica Gel. A solution of 1.44 g of **9a** in toluene was put on a silica gel (80 g) column and kept on column for 70 hr, and then eluted with a mixture of toluene and ethyl acetate (9:1). The first fractions contained the pure 3β-chlorocepham (**18a**) (0.53 g, 40%): ir ($CHCl_3$) 1790, 1780, 1739, and 1728 cm^{-1}.

Next fractions contained 0.76 g (50%) of a mixture of **9a** and **18a** in the 1:1 ratio.

Rearrangement of a Penam 11b to a Cepham 19b and the Conversion of the Latter into 3-Cephem 2b. A solution of 1.12 g (2 mmol) of **11b** in 3 ml of DMF was stirred at room temperature for 20 hr. The precipitate was filtered and discarded. To the filtrate 10 ml of cold water was added, and the solid product was filtered and washed with water and 1 *N* HCl. After drying 0.95 g of crude **19b** was obtained. When this product was chromatographed over silica gel column (1 × 12 in.) and eluted with a mixture of toluene and ethyl acetate (9:1), 594 mg (62%) of **2b** was collected. Crystallization from $CHCl_3$–cyclohexane gave crystals melting at 192–193°: *m/e* 479, 451, 433, 293, and 187.

Rearrangement of *p*-Methoxybenzyl 6β-Phthalimido-2β-nitrooxymethyl-2α-methylpenam-3-carboxylate (15c) to 17c. *p*-Methoxybenzyl 6β-phthalimido-2β-nitrooxymethylpenam-3-carboxylate (**15c**) (80 mg) was dissolved in 0.25 ml of $CDCl_3$ and 2 drops of DMF-d_7. The resulting mixture was heated in a refluxing acetone bath for 1 day. NMR shows conversion to *p*-methoxybenzyl 7-phthalimido-3β-nitrooxy-3α-methylcepham-4-carboxylate (**17c**): *m/e* 464 (M − HNO_3), 436, 361, 343, 300; ir ($CHCl_3$) 1795, 1780, 1742, 1730 cm^{-1}.

***p*-Nitrobenzyl 6β-Phenoxyacetamido-2α-methyl-2β-chloromethylpenam-3-carboxylate (22).** A solution of *p*-nitrobenzyl 7-phenoxyacetamido-3-hydroxy-3-methylcepham-4-carboxylate (**21**) (1.5 g, 3 mmol), thionyl chloride (0.45 ml, 5.5 mmol), and 2 ml of dimethylformamide in 180 ml of dry benzene is heated to reflux under anhydrous conditions for 30 min. The mixture is cooled and evaporated in vacuo to dryness. The resulting red oil is dissolved in 120 ml of ethyl acetate, washed with water (2 × 100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated in vacuo to give a dark foam. The crude product is chromatographed on an acid washed silica gel column (24 × 3 cm) developed with 7% ethyl acetate in benzene (20-ml fractions).

Evaporation in vacuo of fractions 61–79 gives 400 mg (25%) of an amorphous solid identified as *p*-nitrobenzyl 6β-phenoxyacetamido-2α-methyl-2β-chloromethylpenam-3-carboxylate (**22**).

Evaporation in vacuo of fractions 80–110 gives 270 mg (17%) of a violet amorphous solid. The NMR spectrum of this solid showed it to be ca. 60% *p*-nitrobenzyl 6β-phenoxyacetamido-2α-methyl-2β-chloromethylpenam-3-carboxylate (**22**).

The 2β-chloromethylpenam (**22**) rearranges in the solid state (amorphous) in a flask at room temperature to the corresponding *p*-nitrobenzyl 7-phenoxyacetamido-3-chloro-3-methylcepham-4-carboxylate (**23**).

The β-chlorocepham product is converted quantitatively to *p*-nitrobenzyl-7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate by its reaction with 1 equiv of triethylamine in chloroform at room temperature.

Methyl 7-Phthalimido-3-methyl-3-cephem-4-carboxylate (2a).

(a) From 3-Nitrooxycepham 17a. Methyl 7-phthalimido-3-nitrooxy-3-methylcepham-4-carboxylate (**17a**) (200 mg, 0.47 mmol) in 3 ml of *N*,*N*-dimethylformamide was heated to reflux for 20 min. After cooling, water (30 ml) and ethyl acetate (30 ml) were added to the reaction mixture. The organic layer was separated and washed with water (2 × 50 ml) and brine (50 ml) and dried ($MgSO_4$). Evaporation in vacuo gave 144 mg (85%) of a light colored foam. An NMR spectrum showed complete conversion to methyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate (**2a**). A foam was recrystallized from 2-propanol and acetone: mp 187–188°; *m/e* 358, 330, 312, 299, 271, 239, 205.

(b) Conversion of 15a with Pyridine. Methyl 6β-phthalimido-2β-nitrooxymethylpenam-4-carboxylate (**15a**) (80 mg, 0.19 mmol) was dissolved in 0.30 ml of pyridine-d_6 and monitored by NMR. The compound is seen to be stable to these conditions at room temperature, but heating on a steam bath for 15 min gives complete conversion to the corresponding methyl 7-phthalimido-Δ^3-deacetoxycephalosporin (**2a**).

(c) Conversion of 17a with Pyridine. Methyl 7-phthalimido-3β-nitrooxy-3α-methylcepham-4-carboxylate (80 mg, 0.19 mmol) was dissolved in 0.30 ml of pyridine-d_6 and monitored by NMR. The spectrum shows complete conversion to methyl Δ^3-deacetoxycephalosporin (**2a**) within 20 min.

Preparation of *p*-Methoxybenzyl 7-Phthalimido-3-methyl-3-cephem-4-carboxylate (2c) via the Corresponding 3-Nitrooxycepham 17c. *p*-Methoxybenzyl 7-phthalimido-3-nitrooxy-3-methylcepham-4-carboxylate (**17c**) (250 mg, 0.47 mmol) in 4 ml of *N*,*N*-dimethylformamide was heated to reflux for 20 min. After cooling, water (40 ml) and ethyl acetate (40 ml) were added to the reaction mixture. The organic layer was separated and washed with water and brine and dried ($MgSO_4$). Evaporation in vacuo gave a light yellow foam (212 mg, 97%) identified as *p*-methoxybenzyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate (**2c**). It was recrystallized from ethyl acetate and crystals melted at 118–121°: $[\alpha]_D$ +41.2° (CH_3CN); ir ($CHCl_3$), 1800, 1785, 1745, and 1735 cm^{-1}; *m/e* 479, 451, 433, 293, 187.

***p*-Nitrobenzyl 7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylate.** *p*-Nitrobenzyl 6-phenoxyacetamido-2α-methyl-2β-bromomethylpenam-3-carboxylate is dissolved in pyridine and the resulting solution is stirred at room temperature for 2 hr. The reaction mixture is evaporated in vacuo to dryness. The product is then taken up in ethyl acetate and washed successively with 1 *N* HCl, water, and brine and dried (Na_2SO_4). Evaporation in vacuo to dryness provides *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate in high yield. The spectral data and mp are in accord with that reported by Chauvette and Pennington.[28]

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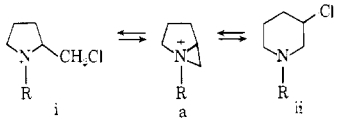

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Electron Spin Resonance Study of Liquids during Photolysis. XIX. Aliphatic Dipeptides[1,2]

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Abstract: Aqueous solutions of simple dipeptides containing about 1% hydrogen peroxide have been photolyzed at room temperature and the resulting radicals studied by electron spin resonance. The peroxide gives ȮH which abstracts hydrogen from the peptide. Abstraction of a hydrogen from the carbon adjacent to the peptide nitrogen to give a single radical occurs in the following cases: glycylglycine, β-alanylglycine, L-alanylglycine, β-alanyl-L-alanine, and glycyl-L-alanine. A mixture of radicals is obtained from glycyl-β-alanine and β-alanyl-β-alanine formed by hydrogen abstraction from each of the CH_2 groups at the carboxylate end of the dipeptide. Hyperfine couplings and *g* values have been measured and are discussed.

We have started a systematic study by electron spin resonance of short-lived radicals at room temperature formed by photolyzing aqueous solutions containing simple peptides and a small amount, ca. 1%, of hydrogen peroxide. Upon photolysis the peroxide gives ȮH which then attacks the peptide by abstracting a hydrogen to give the observed radical. Attack by ȮH is of basic importance in radiation biology. Its formation from H_2O_2 has frequently been used in our photolytic studies, and, with few exceptions, its action has been the abstraction of hydrogen from the substrate. The seven dipeptides studied here contain the simplest aliphatic amino acids: glycine, L-alanine, and β-alanine. All of the spectra exhibit abundant hyperfine splittings leading in most cases to a detailed analysis with identification of the radicals. The nature of the ȮH attack is similar in all of the cases presented, a feature, however, that should not be generalized to more complex dipeptides. The peptides were synthesized by one of the authors (D.G.D.) and thus far have been primarily studied in aqueous solution at or near the pH of the isoelectric point; they were present as zwitterions.

Experimental Section

The spectrometer operated at a nominal frequency of 9.5 GHz and used 100-kHz field modulation. Magnetic field strength was measured by proton magnetic resonance, and this resonance frequency and the microwave frequency were measured with a frequency counter. Further details of the sample handling operations, the equipment, and method of measuring hyperfine couplings and *g* values are described in earlier papers of this series.[2] Estimated error limits of hyperfine couplings and *g* values are ±0.03 G and ±0.00004, respectively, unless otherwise stated. The solutions, typically a few grams of the dipeptide in 25 ml of water, contained about 1% H_2O_2 (added as 98% H_2O_2). Adjustments in pH were