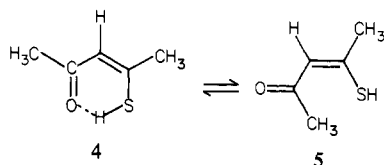


C=O (1710 cm^{-1}), and C=C (1621 cm^{-1}) stretches for **24** is obtained as a primary product from **22** by irradiating AA with light λ 300 nm. This nonchelated primary product undergoes further photochemistry to other species possessing carbonyl absorption at 1692 and 1680 cm^{-1} .^{51,52} However, we cannot marshal any evidence from our matrix-isolation experiments, indicating the involvement of a β -diketone **23** in the photochemistry of AA. We speculate that the path by which **23** is formed during conventional, continuous photolysis of **22**, as described by Fischer, involves geometrical isomerization of a *Z* to an *E* form (Scheme II). Under flash conditions at 25 °C the conformer **24** rapidly reverts only to chelate **22**, the tautomerization to the diketone **23** being considerably slower. But under continuous photolysis, a steady-state concentration of **24** may be produced which is further converted photochemically to **25**. It is probable [judging from the reported experimental value of ΔG^\ddagger for **17** (Table III) and the stability of the enolic ether analogous to **25**⁵⁰] that the thermal unimolecular geometrical isomerization of **25** is too slow to compete with tautomerization of **25** to the diketone **23**. The latter is photochemically stable under these conditions.

Summary

In summary, the evidence favors the following description for the TAA system. At room temperature the dominant enethiol **4** is in rapid equilibrium (NMR time scale) with its nonchelated conformer **5**. Irradiation of matrix-isolated TAA at λ 350 nm



leads to a steady state dominated by **5**, which reverts to the starting chelate either upon irradiation with $\lambda \sim 300$ nm or thermally above 130 K.

(51) A. Krantz and J. Gebicki, unpublished results.

(52) The primary photoproduct of matrix-isolated **22**, which we tentatively regard as **24**, undergoes further reaction, with light at λ 250 and 300 nm and is most reactive at the lower wavelength end of this range.

There is no obvious evidence for the chelated enol **9** in either starting material or in the photolysate, although small amounts may be undetectable by our techniques.

Experimental Section

Proton NMR spectra were recorded on a Varian Associates EM 360 or HFT-80 Spectrometer. Infrared spectra of matrix-isolated species were obtained with a Perkin-Elmer Model 180 spectrophotometer in the constant I_0 mode. Ultraviolet spectra were measured with a Varian Associates Techtron spectrometer.

A Displex, closed cycle, two-stage refrigerator, Model CS 202, manufactured by Air Products and Chemicals Inc., was utilized in these studies. Commercial grade helium (grade 6) was employed as the refrigerant.

A cesium iodide plate in contact with a copper block with indium O-rings supported the matrix deposit for infrared spectral studies. The infrared transmitting outer windows were also cesium iodide. Suprasil quartz plates served as windows for photolysis. The temperature of the sample window was monitored with a chromel-gold-0.07 atom-% iron thermocouple.

Photochemical Reactions. Photochemical reactions were carried out with a 1000-W mercury-xenon lamp (Hanovia No. B977B0010) as the light source. Interference filters (Oriel Corp. of America, No. G-572-09, Stamford, Ct) were used as indicated. Samples, which were prepared and isolated by standard procedures,⁵³ were cooled to 12 K and then irradiated.

The sample was deposited at the rate of 0.4 torr/min. All photochemical experiments, unless otherwise indicated, were carried out at 12 K. Gaseous samples ranged in M/R (matrix host/guest) from 100-1000.

Chemicals. Monothioacetylacetone (TAA) was prepared by the method of Duus and Anthonsen.⁹ TAA was purified by gas chromatography, using a column containing 15% SE-30 on 80/100 mesh Chromosorb W (5 ft \times 1/4 in.), maintained at 117 °C with a carrier gas flow of 25 mL/min. The peak that had a retention time of 5 min was resealed and used for preparation of the sample. Monothioacetylacetone-*d*₂ was prepared as described by Gray and co-workers.⁶

Acknowledgment. We gratefully acknowledge generous financial support from the National Science Foundation, Grant No. CHE 7811563. We are especially appreciative of synthetic work in connection with this project performed by Dr. H. Nickels.

(53) Krantz, A.; Lauren, J. *J. Am. Chem. Soc.* **1981**, *103*, 486.

Structure, Reactivity, and Biological Activity of Strained Bicyclic β -Lactams

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Contribution from the Woodward Research Institute, 4002 Basel, Switzerland, and Physical Research Laboratories, Ciba-Geigy Ltd., 4002 Basel, Switzerland. Received October 27, 1980

Abstract: The antibacterial activities of the structurally simple but highly strained β -lactam compounds **1a**, **2a**, and **3a** are discussed on the basis of their chemical reactivity and the molecular geometry of their crystalline acetyl esters. The nature of the hydrolysis products of **1a**, **2a**, and **3a** was also determined. It was found that the Δ^2 double bond is essential for biological activity.

Introduction

The synthesis of β -lactam derivatives which are more effective than the existing antibiotics has become a subject of worldwide pharmaceutical and commercial interest. However, in spite of the significance of this class of compounds in chemotherapy, little is known about the fundamental factors contributing to their antibiotic potency.

It has been demonstrated¹ that the penicillins and cephalosporins are able to interfere in the terminal step of the bacterial cell wall

biosynthesis. With concomitant cleavage of their labile β -lactam bond, they acylate certain enzymes which direct the cross-linking of linear peptidoglycan strands and thus prevent the buildup of

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† Deceased July 8, 1979.

‡ Ciba-Geigy.

(1) (a) C. H. Callaghan and P. W. Muggleton in "Cephalosporins and Penicillins", H. Flynn, Ed., Academic Press, New York and London, 1972, p 470; (b) D. J. Tipper and J. L. Strominger, *Proc. Natl. Acad. Sci.*, **54**, 1133 (1965); (c) E. M. Wise, Jr., and J. T. Park, *ibid.*, **54**, 75 (1965); (d) K. Izaki, M. Matsuhashi, and J. L. Strominger, *ibid.*, **55**, 656 (1966); (e) J. L. Strominger, K. Izaki, M. Matsuhashi, and D. J. Tipper, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **26**, 9 (1967); (f) K. Izaki, M. Matsuhashi, and J. L. Strominger, *J. Biol. Chem.*, **243**, 3180 (1968). (g) D. J. Tipper and J. L. Strominger, *ibid.*, **243**, 3169 (1968).

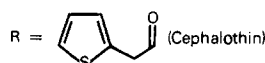
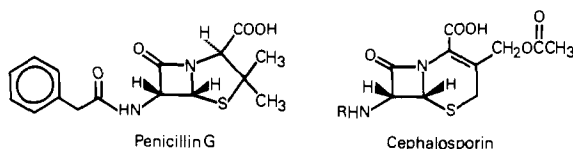
Table I. IR Absorption and Bond Lengths of Bicyclic β -Lactams (Acetyl Ester)

| compound | C=O stretching frequency, cm^{-1} | bond lengths, ^a Å | |
|-----------------------------|--|------------------------------|---------|
| | | OC-N | N-C (3) |
| 1b (penem) | 1798 | 1.419 | 1.427 |
| 2b (Δ^2 carbapenem) | 1785 | 1.419 | 1.438 |
| 3b (Δ^1 carbapenem) | 1778 | 1.402 | 1.463 |
| penicillins ³ | ~1775 | 1.37 | 1.46 |
| cephalosporins ³ | ~1770 | 1.38 | 1.40 |

^a Maximum standard deviation for 1b, 2b, and 3b (± 0.006 Å).

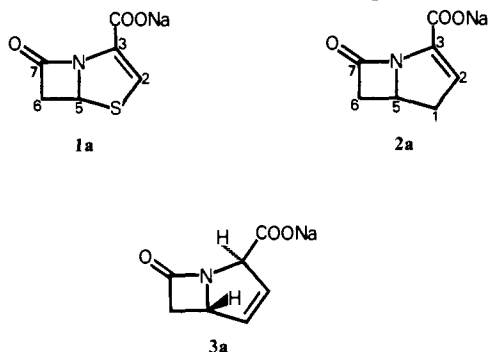
the peptide bridges, essential for the structural strength of the cell walls.

This suggests that, among the many possible factors which make an antibiotic effective, one structural and one chemical feature is most typical: The *molecular geometry* should be such that the antibiotic will be mistakenly recognized by the transpeptidase enzyme as a normal substrate. On the other hand, its *chemical reactivity* should be significantly high in order to allow the acylation of the nucleophilic enzyme.



The high reactivity of the penicillins was postulated² as early as 1949 to be a consequence of the *hindered amide resonance* which arises from the pyramidal geometry of the β -lactam nitrogen. In the cephalosporins having less ring strain, a *competitive enamine resonance*, resulting from the delocalization of the nitrogen atom's unshared electron pair into the adjacent dihydrothiazine π system, is thought³ to activate the β -lactam, thus facilitating nucleophilic attack at the carbonyl group.

With the discovery of the new nonclassical β -lactam antibiotics, i.e., the penems and the Δ^2 carbapenems, the question arises whether the same resonance features are responsible for the chemical reactivity and possibly also for the antibacterial activity. We wish to disclose here the results found with three simple, racemic representatives **1a**, **2a**, and **3a**. These models lack any additional and interfering side chains at the 2 or 6 positions and seemed particularly suitable for our investigations.



Syntheses

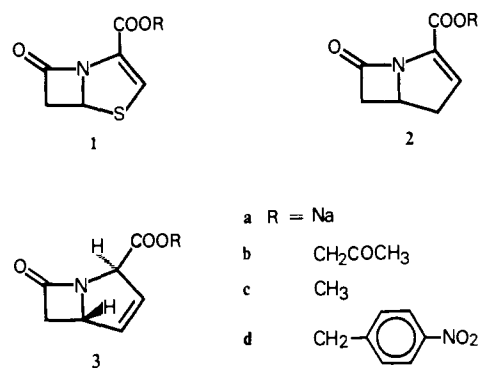
From our earlier experience⁴ in the penem field we had found that acetyl esters crystallize easily, and this suggested that we

(2) R. B. Woodward in "The Chemistry of Penicillin", H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N.J., 1949, p 440.

(3) (a) R. M. Sweet in ref 1a, p 280; (b) R. M. Sweet and L. F. Dahl, *J. Am. Chem. Soc.*, **92**, 5489 (1970).

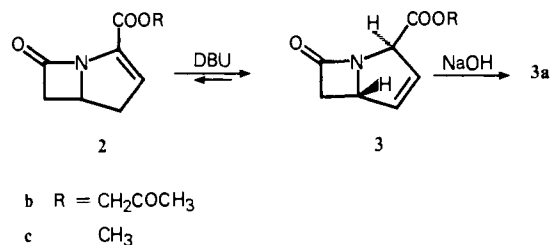
(4) H. R. Pfandler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, **101**, 6306 (1979).

choose the esters **1b**, **2b**, and **3b**, rather than the (unstable) acids or sodium salts for our structural investigations. The latter were prepared then by mild saponification.



The free acid of the penem derivative **1a** has been prepared and reported⁴ from our laboratories. Syntheses of 1-carbapen-2-em-3-carboxylic salts and esters have recently been disclosed by a Merck group^{5a} and later by Beecham chemists.⁶ We have found the procedure of the latter group to be very satisfactory and adopted it for the preparation of the corresponding acetyl ester **2b**. The deprotection of the methyl ester **2c** by alkaline hydrolysis resulted in extensive decomposition of the labile β -lactam system, whereas the same reaction with the acetyl ester **2b** provided a somewhat better result.

Δ^2, Δ^1 -Isomerization has already been observed⁷ with thienamycin derivatives. Similarly, using DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) as a base, **2b** and more efficiently the methyl ester **2c** isomerized affording Δ^1, Δ^2 mixtures after prolonged standing in tetrahydrofuran at room temperature. This reaction was found to be slower than the related Δ^3, Δ^2 -isomerization of cephalosporin esters. After deprotection both 1-carbapen-1-em-carboxylic esters **3b** and **3c**, afforded our third parent compound, the novel sodium 1-carbapen-1-em-3-carboxylate (**3a**) in essentially quantitative yield. Attempts to isolate the free carboxylic acid of **3a** led to complete decomposition of the β -lactam.



Structures

According to the formalism of Sweet and Dahl,³ the critical departure from coplanarity of the β -lactam nitrogen with its three substituents is conveniently expressed by the altitude of a pyramid, having N-4 as apex and C-3, C-5, and C-7 as base. With our crystalline esters **1b**,⁸ **2b**, and **3b** the X-ray structure determinations revealed pyramids with the very high altitudes of 0.42, 0.50, and 0.54 Å, respectively (see Figure 1 and Table II).

The mean OC-N bond lengths (see Table I) were very close to 1.42 Å. Compared to the penicillins (1.37 Å) and the cephalosporins (1.38 Å),³ a more pronounced single bond character

(5) (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978). (b) We are grateful to Dr. P. Schneider (Ciba-Geigy Ltd.) for supplying the minimal inhibitory concentration values of compound **2a**.

(6) (a) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 236 (1979); (b) German Offen. 28 11 514, 1978, p 118.

(7) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).

(8) The X-ray investigation initially served to establish the absolute configurations of the optically active forms of **1b** and was carried out on the 5S penem. For an easier comparison, the X-ray model has been transformed to its mirror image in this paper.

Table II. Pyramidal Character, Chemical Reactivity, and Antibacterial Activity of Bicyclic β -Lactams

| compound | altitude of pyramid, ^a Å | chemical half-life, ^b h | minimal inhibitory concentration (MIC), $\mu\text{g/mL}^c$ | | | |
|---|-------------------------------------|------------------------------------|--|-----------------------|-----------------------------|---------------------|
| | | | St a ^d | St a res ^e | <i>E. coli</i> ^f | Ps aer ^g |
| 1a (<i>rac</i> -penem) | 0.42 | 20 | 8 | 8 | 4 | 16 |
| 2a (<i>rac</i> - Δ^2 -carbapenem) | 0.50 | ~3 | 16 | 16 | 16 | 64 |
| 3a (<i>rac</i> - Δ^1 -carbapenem) | 0.54 | 70 | >128 | >128 | >128 | >128 |
| penicillins | ~0.40 | | 0.01 | 32 | 16 | >128 |
| cephalosporins | ~0.24 | | 0.1 | 0.5 | 8 | >128 |

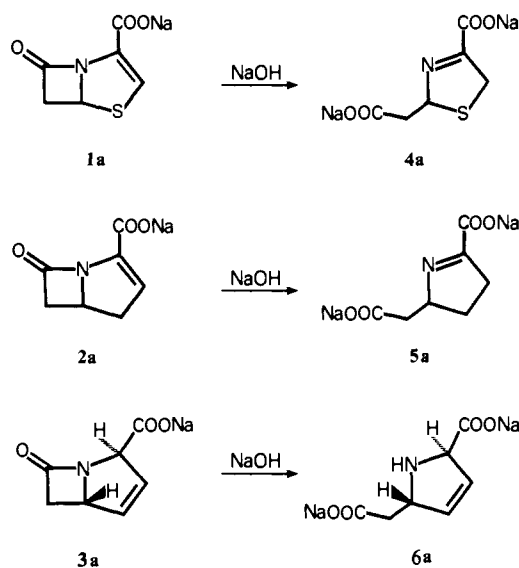
^a Having N-4 as apex and C-3, C-5, and C-7 as base or corresponding atoms: determined on the crystalline esters 1b, 2b, and 3b. The values for the penicillins and cephalosporins are reported.³ ^b In phosphate buffer pH 7.4⁹ at 37 °C. ^c VST agar; inoculum ca. 10^4 cells/mL; pH 7.4. A MIC of 2 for the racemic compounds corresponds⁴ to that of 1 for the optically active penicillin G and cephalothin. ^d *Staphylococcus aureus* 10 B. ^e *Staphylococcus aureus* 2999i⁺p⁺ (penicillin resistant). ^f *Escherichia coli* 205. ^g *Pseudomonas aeruginosa* ATCC 12055.

and a low degree of amide resonance is therefore indicated.

The bond lengths of the adjacent N-C(3) bonds are slightly longer (near 1.43 Å) in the conjugated species 1b and 2b than that of the cephalosporins (1.40 Å), pointing to a weaker enamine resonance. The existence of such a resonance is confirmed by the higher carbonyl stretching frequency of the Δ^2 carbapenem 2b compared to that of the isomeric 3b.

Hydrolyses

The nature of the hydrolysis products of the new nonclassical



β -lactams has never been investigated. Our representatives 1a, 2a, and 3a were therefore hydrolyzed with aqueous NaOH. Unfortunately, the direct isolation of the resulting products proved difficult. Thus the crude reaction products were freeze-dried and subsequently alkylated with *p*-nitrobenzyl bromide. The resulting ester derivatives 4d, 5d, and 6d allowed the characterization of the intermediates. Whereas the Δ^1 -carbapenem 3a afforded the expected product 6a, from simple β -lactam cleavage, the hydrolyses of 1a and 2a were accompanied by double bond migration furnishing the UV-inactive products 4a and 5a.

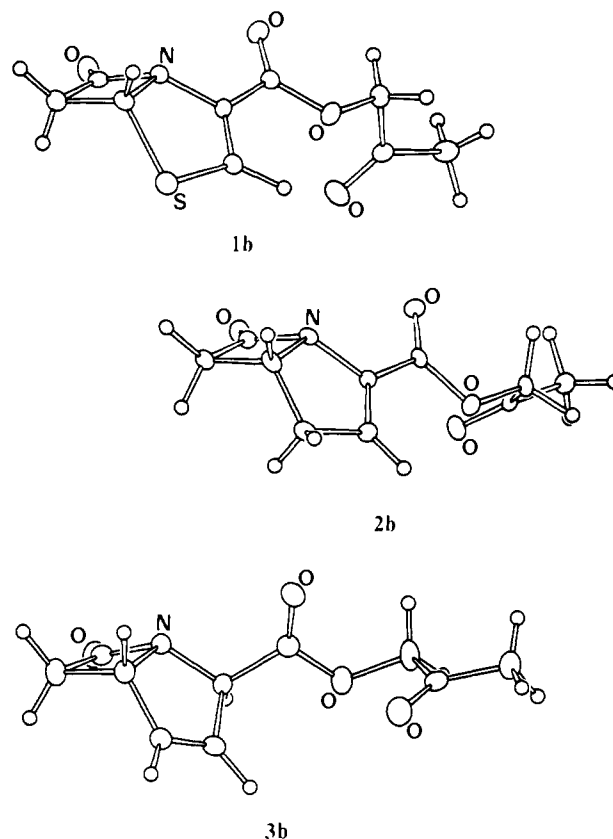
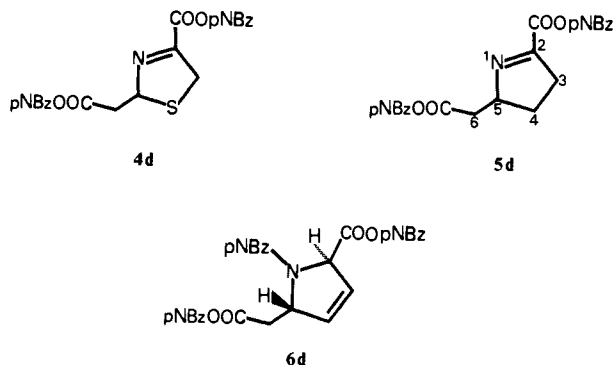


Figure 1. X-ray models of bicyclic β -lactam compounds (acetonyl esters).

For compounds 1a and 2a the determination of the reaction rates of the above-mentioned hydrolyses was followed by using the characteristic UV absorptions,⁹ but for the unconjugated 3a, having no significant UV chromophore, the reaction was monitored by NMR spectroscopy in deuterated buffer solution. Thus, the determined half-lives were 20, 3, 70 h, respectively (see Table II).

Biological Activities

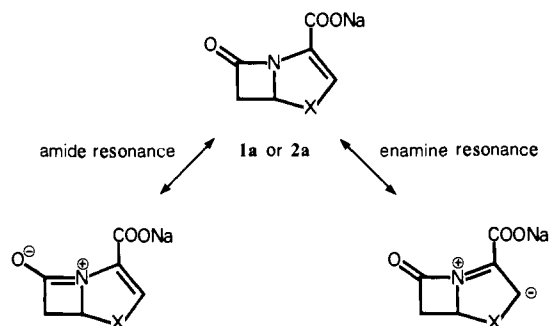
The penem 1a as well as its nuclear analogue 2a are known to show broad antibacterial activity (Table II).^{4,5} The novel Δ^1 -carbapenem 3a, however, was found to be inactive against 30 types of bacteria including Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) strains. Moreover, no significant β -lactamase inhibiting character of 3a was determined.¹⁰

(9) The biologically active *threo-trans*-6-(α -hydroxyethyl)penem-3-carboxylic acid, for example, has a chemical half-life of 105 h under the same conditions: H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, **102**, 2039 (1980).

(10) Our most recent investigations show that 3a is not recognized by two bacterial enzymes: 3a was unaffected by the β -lactamases penicillinase Riker and *E. coli* R 16 TEM, at conditions where penicillin G was immediately hydrolyzed (by both enzymes) and the penem 1a was partially hydrolyzed (by the *E. coli* enzyme).

Discussion

From our structural investigations it became evident that the parent compounds **1a**, **2a**, and **3a** possess a high degree of structural strain, arising from the combination of four- and five-membered rings. One might have expected that the exceptionally strained Δ^1 -carbapenem **3a** would be the most chemically reactive. However, as shown in Table II, it was found to be the most stable among our representatives. This outcome can be explained by the inability of **3a** to delocalize the unshared nitrogen electron pair into a π -orbital system. These electrons are delocalized into the carbonyl group and strengthen the lactam bond. With both compounds **1a** and **2a**, on the other hand, the enamine resonance is possible and contributes, additionally to the hindered amide resonance arising from the pyramidal geometry of the nitrogen, to the ease of β -lactam hydrolysis.



The outstanding biological activity of penicillins and cephalosporins has been correlated³ with the increased chemical reactivity of their β -lactam systems, as compared to that of simple, monocyclic, azetidiones. The β -lactam reactivity of all three parent compounds, **1a**, **2a**, and **3a**, as judged by their hydrolytic half-life values, compare well with those of the above-mentioned, potent antibiotics.⁹

Another condition as well, often connected with the antibiotic activity of penicillins and cephalosporins, i.e., the pronounced pyramidal architecture of the β -lactam system, is fulfilled with all three of our compounds. However, only two of them, i.e., **1a** and **2a**, proved biologically active. Despite having the highest nitrogen pyramid ever determined, **3a** was found inactive.

Thus, high chemical reactivity of the β -lactam and pyramidal geometry of the β -lactam nitrogen are *not sufficient prerequisites for antibiotic activity* in this group of compounds.

Experimental Section

Melting points (Kofler) are uncorrected. All IR spectra were recorded in CH_2Cl_2 on a Perkin-Elmer 710B or 580B spectrometer, and all NMR spectra in CDCl_3 (with Me_4Si as internal standard) on a Varian XL-100 or a Bruker HX-360 spectrometer (chemical shifts are reported in δ values) unless otherwise mentioned. UV spectra were recorded on a Beckman DB-GT spectrometer. All R_f values were determined on Merck silica gel 60 F_{254} TLC plates.

A. Preparation of Parent Compounds. Sodium Penem-3-carboxylate (1a). To a stirred solution of racemic penem-3-carboxylic acid⁴ (17.1 mg, 0.1 mmol) in a mixture of acetonitrile (3 mL) and water (1 mL) at 0 °C aqueous NaOH (0.1 N, 1 mL, 0.1 mmol) was added and the resulting solution freeze-dried under high vacuum (0.005 mm). Colorless noncrystalline **1a** (19.4 mg, 100%) was thus obtained: UV (H_2O) λ_{max} 260 nm (ϵ 3000), 308 nm (ϵ 5700).

Acetonyl (4-Allylazetididin-2-on-1-yl)hydroxyacetates (Epimeric Mixture). A solution of racemic 4-allylazetididin-2-one⁶ (2.22 g, 20 mmol) and acetonyl glyoxylate⁴ (6.7 g, 50 mmol) in a mixture of toluene (33 mL) and DMF (17 mL) was stirred overnight at 40 °C with molecular sieves (4 Å, 60 g). The mixture was then filtered and the residual sieves were washed with ethyl acetate. The combined filtrate and washings were evaporated in vacuo and the residue was stirred under high vacuum (0.005 mm) at 60 °C until the weight was \sim 4.6 g (\sim 100%). A noncrystalline oil was thus obtained, R_f 0.3 (AcOEt): IR (CH_2Cl_2) 3550, 2950, 1760, 1740, 1365, 1160 cm^{-1} .

Acetonyl (4-Allylazetididin-2-on-1-yl)chloroacetates (Epimeric Mixture). To a solution of crude acetonyl (4-allylazetididin-2-on-1-yl)hydroxyacetates (4.6 g, 20 mmol) in dry tetrahydrofuran (100 mL) are added at -15 °C thionyl chloride (2.81 g, 1.72 mL, 23.6 mmol) and subsequently triethylamine (2.41 g, 3.32 mL, 23.8 mmol). The reaction mixture was

stirred at 0 °C for 30 min, diluted with methylene chloride (500 mL) and then washed with ice-cold 0.1 N HCl solution (300 mL), followed by saturated NaCl solution (300 mL). The organic layer was dried over Na_2SO_4 and filtered; the solvent was removed in vacuo leaving the title compounds (4.95 g, \sim 100%) as a pale yellow noncrystalline solid: R_f 0.43 (AcOEt); IR (CH_2Cl_2) 3050, 2950, 1765, 1740, 1360, 1160 cm^{-1} .

Acetonyl (4-Allylazetididin-2-on-1-yl)triphenylphosphoranylideneacetate. A solution of crude acetonyl (4-allylazetididin-2-on-1-yl)chloroacetates (4.95 g, 20 mmol) and triphenylphosphine (10.5 g, 40 mmol) in dry THF (9 mL) was kept under nitrogen at 5 °C for 4 days. The reaction mixture was diluted with methylene chloride (100 mL) and washed twice with portions (100 mL) of 10% aqueous Na_2CO_3 solution. The organic layer was dried over Na_2SO_4 and filtered; the solvent was removed in vacuo. The residue was chromatographed on Merck silica gel (200 g) with toluene-AcOEt (1:1) (25 fractions, 200 mL each). A white crystalline title compound (4.85 g, 50%) was thus obtained. A sample was recrystallized from methylene chloride-ether: mp 194–196 °C; R_f 0.24 (AcOEt); IR (CH_2Cl_2) 3050, 2920, 1740, 1625, 1440, 1110 cm^{-1} . Anal. Calcd for $\text{C}_{29}\text{H}_{28}\text{NO}_4\text{P}$ (485.52): C, 71.74; H, 5.81; N, 2.88. Found: C, 71.90; H, 5.81; N, 3.07.

Acetonyl 1-Carbapen-2-em-3-carboxylate (2b). Into a solution containing acetonyl (4-allylazetididin-2-on-1-yl)triphenylphosphoranylideneacetate (971 mg, 2 mmol) and trifluoroacetic acid (1 mL) in methylene chloride (30 mL) at -50 °C, ozone in oxygen was introduced during 2 h at a rate of 0.33 mmol/min. The excess ozone was removed by passing N_2 through the solution for 2 min. Dimethyl sulfide (2 mL) was added and the mixture stirred at room temperature for 20 min (until the starch iodide test became negative). Ice-cold methylene chloride (300 mL) was added and the mixture washed twice carefully with two portions (100 mL) of cold aqueous 10% KHCO_3 solution. The organic layer was dried over Na_2SO_4 and filtered, the solvent removed in vacuo, and the residue dried under high vacuum for 2 min. It was redissolved in methylene chloride (20 mL filtered through Alox) and the solution kept at room temperature for 1.5 h. After this period the Wittig condensation was completed. The solvent was removed in vacuo and the residue quickly chromatographed on silica gel (50 g, acid washed) with toluene-AcOEt (2:1) (20 fractions 30 mL each). Thus, pure crystalline title compound (330 mg, 79%) was obtained: mp 86–87 °C (ether-pentane); R_f 0.32 (AcOEt); UV (EtOH) λ_{max} 271 nm (ϵ 4800); IR (CH_2Cl_2) 3060, 2950, 1785, 1740, 1730, 1610, 1165 cm^{-1} ; NMR (acetone- d_6) δ 2.15 (s, 3), 2.8–3.7 (m, 4), 4.30 (m, 1), 4.80 (s, 2), 6.60 (t, 1, $J = 3.5$ Hz). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_4$ (209.20): C, 57.42; H, 5.30; N, 6.70. Found: C, 57.55; H, 5.55; N, 6.92. The structure of **2b** was confirmed by X-ray analysis.

Sodium 1-Carbapen-2-em-3-carboxylate (2a) (in Solution). To a stirred solution of acetonyl 1-carbapen-2-em-3-carboxylate (41.8 mg, 0.2 mmol) in acetonitrile (4 mL) at 0 °C, within 5 min aqueous NaOH (0.1 N, 2 mL, 0.2 mmol) was added and the mixture stirred at 0 °C for additional 5 min. The resulting solution was immediately used for further investigations: UV (H_2O) λ_{max} 261 nm (E of 10^{-4} M solution = 0.36).

Acetonyl 1-Carbapen-1-em-3-carboxylate (3b). A solution containing acetonyl 1-carbapen-2-em-3-carboxylate (209 mg, 1 mmol) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 613 mg, 600 μL , 4 mmol) in dry (refluxed and distilled over LiAlH_4) THF (20 mL) was kept at room temperature for 90 min. The reaction mixture was diluted with toluene (100 mL) and washed subsequently with aqueous HCl (0.5 N, 50 mL) and saturated NaCl (50 mL) solutions. The organic layer was dried over Na_2SO_4 and filtered and the solvent removed in vacuo. Chromatography of the residue on Merck silica gel (20 g) with toluene-AcOEt (2:1) (15 fractions, 10 mL each) afforded the title compound **3b** (16.7 mg, 8%): mp 68–69 °C (CH_2Cl_2 -pentane); R_f 0.42 (AcOEt); IR (CH_2Cl_2) 3060, 2940, 1778, 1760, 1738, 1170 cm^{-1} ; NMR (CDCl_3) δ 2.14 (s, 3), 2.88 (dd, 1, $J = 3.5$, 16 Hz), 3.47 (dd, 1, $J = 6$, 16 Hz), 4.60 (m, 1), 4.68 (AB q, 2), 5.30 (m, 1); 6.20 (m, 2). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_4$ (209.20): C, 57.42; H, 5.30; N, 6.70. Found: C, 57.25; H, 5.21; N, 6.97. The structure of **3b** was confirmed by X-ray analysis.

Methyl 1-Carbapen-1-em-3-carboxylate (3c). A solution containing crystalline methyl 1-carbapen-2-em-3-carboxylate (**2c**)⁶ (1.002 g, 6 mmol) and DBU (4.08 g, 4 mL, 27 mmol) in dry (refluxed and distilled over LiAlH_4) THF (100 mL) was kept under nitrogen for 24 h at room temperature. The solution was diluted with toluene (600 mL) and washed subsequently with cold aqueous solutions of 5% citric acid (300 mL) and saturated NaCl (300 mL). The aqueous layer was extracted with methylene chloride (200 mL), and the combined organic layers were dried over Na_2SO_4 . Filtration and evaporation of the solvent in vacuo gave a residue which was chromatographed on Merck silica gel (60 g) with toluene-AcOEt (3:1) (20 fractions, 30 mL each). Pure crystalline Δ^1 isomer **3c** (370 mg, 37%) was eluted first: mp 37–38 °C; R_f 0.5 (AcOEt); IR (CH_2Cl_2) 3050, 2940, 1775, 1750 cm^{-1} ; NMR (CDCl_3) δ 2.90 (dd, 1, $J = 3$, 17 Hz), 3.45 (dd, 1, $J = 6$, 17 Hz), 3.73 (s, 3), 4.58

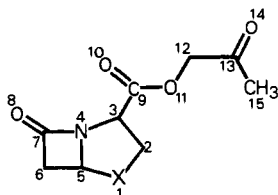
Table III. Final Atomic Coordinates for Acetylonyl Penem-3-carboxylate (1b)

| atom | X/A | Y/B | Z/C |
|-------|------------|------------|-------------|
| S(1) | 0.0868 (2) | 0.1951 (1) | 0.1363 (0) |
| C(2) | 0.3140 (6) | 0.2875 (3) | 0.0892 (2) |
| C(3) | 0.4570 (6) | 0.3704 (3) | 0.1273 (1) |
| N(4) | 0.3965 (5) | 0.3678 (2) | 0.2001 (1) |
| C(5) | 0.2226 (6) | 0.2566 (3) | 0.2197 (2) |
| C(6) | 0.0686 (6) | 0.3532 (3) | 0.2646 (2) |
| C(7) | 0.2438 (6) | 0.4621 (4) | 0.2370 (2) |
| O(8) | 0.2607 (5) | 0.5822 (2) | 0.2416 (1) |
| C(9) | 0.6631 (6) | 0.4584 (3) | 0.1022 (2) |
| O(10) | 0.7755 (4) | 0.5393 (2) | 0.1374 (1) |
| O(11) | 0.7113 (5) | 0.4359 (2) | 0.0339 (1) |
| C(12) | 0.8906 (7) | 0.5241 (3) | 0.0001 (2) |
| C(13) | 0.7509 (7) | 0.6204 (3) | -0.0478 (2) |
| O(14) | 0.5261 (5) | 0.6422 (3) | -0.0410 (1) |
| C(15) | 0.9143 (8) | 0.6840 (4) | -0.1017 (2) |
| H(16) | 0.372 (6) | 0.293 (3) | 0.033 (1) |
| H(17) | 0.317 (5) | 0.193 (3) | 0.237 (1) |
| H(18) | 0.069 (6) | 0.338 (3) | 0.315 (1) |
| H(19) | -0.083 (6) | 0.358 (3) | 0.247 (1) |
| H(20) | 1.000 (6) | 0.595 (3) | 0.027 (1) |
| H(21) | 0.994 (6) | 0.454 (3) | -0.031 (1) |
| H(22) | 0.813 (6) | 0.706 (3) | -0.147 (1) |
| H(23) | 0.990 (8) | 0.774 (3) | -0.081 (1) |
| H(24) | 1.064 (7) | 0.618 (3) | -0.115 (2) |

(m, 1), 5.22 (m, 1), 6.15 (m, 2). Anal. Calcd for $C_8H_9NO_3$ (167.16): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.54; H, 5.37; N, 8.55. Then pure Δ^2 isomer **2c** (60 mg, 6%) was eluted: mp 69–71 °C (lit.⁶ 72–72.5 °C); R_f 0.41 (AcOEt); UV (EtOH) λ_{max} 269 nm (ϵ 4650); IR (CH_2Cl_2) 3050, 2940, 1783, 1725, 1605, 1215 cm^{-1} ; NMR (acetone- d_6) 2.8–3.6 (m, 4), 3.72 (s, 3), 4.25 (m, 1), 6.50 (t, 1, $J = 3$ Hz). Anal. Calcd for $C_8H_9NO_3$ (167.16): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.50; H, 5.44; N, 8.47.

Sodium 1-Carbapen-1-em-3-carboxylate (3a). To a stirred solution of methyl 1-carbapen-1-em-3-carboxylate (**3c**, 83.5 mg, 0.5 mmol) in a mixture of acetonitrile (15 mL) and water (5 mL) at 0 °C within 20 min aqueous NaOH (0.1 N, 5 mL, 0.5 mmol) was added and the mixture stirred for additional 10 min at 0 °C. Freeze-drying of the solution under high vacuum afforded pure title compound **3a** (87.5 mg, ~100%) as a noncrystalline solid: R_f 0.55 (H_2O reverse-phase TLC L 254, OPTI-UP C 12; supplier ANTEC Ltd., 4431 Bennwil, Switzerland); NMR (D_2O) δ 2.87 (dd, 1, $J = 3.5, 16$ Hz), 3.38 (dd, 1, $J = 6, 16$ Hz), 4.54 (m, 1), 4.96 (m, 1), 6.12 (m, 2). For further characterization **3a** was converted into **p-nitrobenzyl 1-carbapen-1-em-3-carboxylate (3d)**. Crude **3a** (58.8 mg, ~0.3 mmol) was dissolved in dry dimethyl sulfoxide (0.3 mL) and with stirring *p*-nitrobenzyl bromide (108 mg, 0.5 mmol) was added; the mixture was stirred at room temperature for 60 min. It was diluted with toluene (15 mL) and washed three times with water (15 mL). The organic layer was dried over Na_2SO_4 and filtered; the solvent was removed in vacuo. The residue was chromatographed on Merck silica gel (4 g) with toluene–AcOEt (3:1), 15 fractions of 4 mL each to give pure **3d** (55 mg, 63%) as a viscous liquid: R_f 0.54 (EtOAc); UV (EtOH) λ_{max} 265 nm (ϵ 9800); IR (CH_2Cl_2) 3060, 2950, 1775, 1750, 1610, 1525, 1350 cm^{-1} ; NMR (CD_3CN) δ 2.78 (dd, 1, $J = 3.5, 16$ Hz), 3.41 (dd, 1, $J = 6, 16$ Hz), 4.50 (m, 1), 5.18 (m, 1), 5.21 (s, 2), 6.18 (m, 2), 7.57 (d, 2, $J = 9$ Hz), 8.20 (d, 2, $J = 9$ Hz). Anal. Calcd for $C_{14}H_{12}N_2O_5$ (288.26): C, 58.33; H, 4.20; N, 9.72. Found: C, 57.99; H, 4.45; N, 9.90.

B. X-ray analyses data for all three compounds were collected on the same Picker FACS-I diffractometer using graphite monochromated Mo K α radiation.



Acetylonyl Penem-3-carboxylate (1b). (*5S*)-Enantiomer crystal data: $a = 5.210$ (1), $b = 9.971$ (2), $c = 19.099$ (3) Å, orthorhombic, space group $P_{21}212$, $Z = 4$. In the range $2^\circ \leq 2\theta \leq 68^\circ$ 2540 independent reflections were measured of which 1743 were considered as observed ($I > 2\sigma(I)$). The structure was solved by conventional Patterson and Fourier techniques. The hydrogen atoms were located in difference maps

Table IV. Final Atomic Coordinates for Acetylonyl 1-Carbapen-2-em-3-carboxylate (2b)

| atom | X/A | Y/B | Z/C |
|-------|------------|------------|-------------|
| C(1) | 0.1232 (6) | 0.4011 (9) | 0.3977 (6) |
| C(2) | 0.2326 (6) | 0.4232 (9) | 0.2662 (6) |
| C(3) | 0.3955 (6) | 0.3311 (7) | 0.2754 (5) |
| N(4) | 0.4082 (5) | 0.2345 (6) | 0.4081 (4) |
| C(5) | 0.2262 (7) | 0.2562 (8) | 0.4806 (5) |
| C(6) | 0.3400 (7) | 0.2967 (9) | 0.6214 (6) |
| C(7) | 0.5159 (8) | 0.2853 (8) | 0.5350 (5) |
| O(8) | 0.6812 (4) | 0.3124 (6) | 0.5540 (4) |
| C(9) | 0.5427 (6) | 0.3076 (7) | 0.1714 (6) |
| O(10) | 0.6759 (5) | 0.2180 (5) | 0.1900 (4) |
| O(11) | 0.5061 (5) | 0.4102 (6) | 0.0532 (3) |
| C(12) | 0.6377 (7) | 0.3876 (9) | -0.0583 (5) |
| C(13) | 0.8173 (6) | 0.4846 (7) | -0.0291 (5) |
| O(14) | 0.8411 (5) | 0.5683 (6) | 0.0776 (4) |
| C(15) | 0.9572 (7) | 0.4638 (9) | -0.1412 (6) |
| H(16) | -0.021 (5) | 0.377 (6) | 0.378 (4) |
| H(17) | 0.129 (5) | 0.498 (7) | 0.455 (4) |
| H(18) | 0.189 (5) | 0.497 (5) | 0.183 (4) |
| H(19) | 0.123 (5) | 0.158 (7) | 0.495 (3) |
| H(20) | 0.314 (5) | 0.212 (6) | 0.709 (4) |
| H(21) | 0.306 (5) | 0.415 (6) | 0.662 (4) |
| H(22) | 0.672 (5) | 0.258 (6) | -0.064 (4) |
| H(23) | 0.579 (5) | 0.438 (6) | -0.162 (4) |
| H(24) | 0.887 (5) | 0.431 (7) | -0.245 (4) |
| H(25) | 1.012 (5) | 0.570 (6) | -0.158 (4) |
| H(26) | 1.055 (5) | 0.366 (6) | -0.099 (4) |

and included in the refinement with isotropic temperature factors. For all other atoms anisotropic temperature factors were introduced. After several cycles the refinement converged to a final value of $R = 0.050$. To determine the correct absolute configuration, 20 Bijvoet¹¹ pairs were measured (using Cu K α radiation) each having a difference of at least 8% based on the anomalous scattering of S. The molecule shown in Figure 1 represents the (*5R*) configuration of the molecule. Final atomic coordinates are given in Table III. The sum of the three nitrogen bond angles is 331.5°. The thiazolidine ring adopts the envelope conformation with C(5) 0.25 Å out of the plane of the other four atoms. The angle between the planes of the double bond N(4), C(3), C(9), C(2), S(1) and the ester group C(3), C(9), O(10), O(11) is 6.4°. ¹²

Acetylonyl 1-Carbapen-2-em-3-carboxylate (2b). Crystal data: $a = 7.086$ (2), $b = 7.817$ (2), $c = 9.227$ (2) Å, $\beta = 93.10$ (1)°, monoclinic, space group P_{21} , $Z = 2$. In the range $2^\circ \leq 2\theta \leq 65^\circ$ 911 independent reflections were measured of which 644 were considered as observed ($I > 2\sigma(I)$). The structure was solved by direct methods using the program system MULTAN 77.¹³ The hydrogen atoms were located in difference maps and included in the refinement with fixed temperature factors. For all the other atoms anisotropic temperature factors were introduced. After several cycles the refinement converged to a final value of $R = 0.047$.¹¹ Final atomic coordinates are given in Table IV. The sum of the three nitrogen bond angles is 324.1°. The pyrrolidine ring adopts the envelope conformation with C(5) 0.20 Å out of the plane of the other four atoms. The angle between the planes of the double bond N(4), C(3), C(9), C(2), C(1) and the ester group C(3), C(9), O(10), O(11) is 1.7°. ¹²

Acetylonyl 1-Carbapen-1-em-3-carboxylate (3b). Crystal data: $a = 9.545$ (2), $b = 15.968$ (3), $c = 6.654$ (2) Å, $\beta = 97.97$ (2)°, monoclinic, space group $P_{21/c}$, $Z = 4$. In the range $2^\circ \leq 2\theta \leq 55^\circ$ 2017 independent

(11) J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature (London)*, **168**, 271 (1951).

(12) Thermal parameters, bond lengths, bond angles, and torsion angles between nonhydrogen atoms are available as supplementary material.

(13) P. Main, L. L. Lessinger, and M. M. Woolfson, Department of Physics, University of York, York, England. G. Germain and J. P. Declercq, Louvain-La-Neuve, Belgique. A system of computer programmes for the automatic solution of crystal structures from X-ray diffraction data.

(14) **Note Added in Proof:** Most recently Dr. W. Zimmermann (Ciba-Geigy Ltd.) has found that unlike all bicyclic β -lactam antibiotics including the optically active (*5R*)-penem-3-carboxylic acid,⁴ the Δ^1 carbapenem **3a** is not a substrate for penicillin binding proteins obtained from *E. coli* KN 126. This suggests that, in the absence of any other side chains, the presence of the Δ^2 double bond is most important for the recognition by the relevant bacterial enzymes and consequently for antibiotic activity.

(15) **Note Added in Proof:** During the printing of this manuscript, a paper on a similar subject appeared (Shih, D. H.; Ratcliffe, R. W. *J. Med. Chem.* **1981**, **24**, 639), the results of which support our conclusion concerning the relative reactivities of the two isomeric carbapenems.

Table V. Atomic Coordinates for Acetylonyl 1-Carbapen-1-em-3-carboxylate (3b)

| atom | X/A | Y/B | Z/C |
|-------|------------|-------------|------------|
| C(1) | 0.4575 (4) | 0.1002 (2) | 0.4765 (5) |
| C(2) | 0.3862 (3) | 0.0967 (2) | 0.6335 (5) |
| C(3) | 0.2263 (3) | 0.0884 (2) | 0.5664 (5) |
| N(4) | 0.2165 (3) | 0.0973 (2) | 0.3460 (4) |
| C(5) | 0.3616 (4) | 0.0931 (2) | 0.2781 (5) |
| C(6) | 0.3252 (4) | 0.1751 (2) | 0.1541 (5) |
| C(7) | 0.1941 (3) | 0.1773 (2) | 0.2611 (5) |
| O(8) | 0.1046 (2) | 0.2289 (2) | 0.2831 (4) |
| C(9) | 0.1767 (3) | 0.0034 (2) | 0.6285 (5) |
| O(10) | 0.1539 (3) | -0.0569 (2) | 0.5234 (4) |
| O(11) | 0.1653 (3) | 0.0057 (2) | 0.8277 (4) |
| C(12) | 0.1290 (4) | -0.0709 (2) | 0.9210 (6) |
| C(13) | 0.2550 (4) | -0.1254 (2) | 0.9853 (5) |
| O(14) | 0.3693 (3) | -0.1088 (2) | 0.9361 (4) |
| C(15) | 0.2278 (4) | -0.1999 (2) | 1.1116 (6) |
| H(16) | 0.570 (4) | 0.099 (2) | 0.495 (5) |
| H(17) | 0.424 (4) | 0.099 (2) | 0.793 (5) |
| H(18) | 0.165 (4) | 0.136 (2) | 0.633 (5) |
| H(19) | 0.371 (4) | 0.038 (2) | 0.177 (5) |
| H(20) | 0.301 (4) | 0.165 (2) | -0.001 (5) |
| H(21) | 0.389 (3) | 0.227 (2) | 0.185 (5) |
| H(22) | 0.088 (4) | -0.054 (2) | 1.054 (5) |
| H(23) | 0.069 (4) | -0.108 (2) | 0.815 (5) |
| H(24) | 0.214 (4) | -0.178 (2) | 1.249 (5) |
| H(25) | 0.139 (3) | -0.225 (2) | 1.048 (5) |
| H(26) | 0.331 (3) | -0.234 (2) | 1.147 (5) |

reflections were measured of which 1522 were considered as observed ($I > 2\sigma(I)$). The structure was solved by direct methods using the program MULTAN 77.¹³ The hydrogen atoms were located in difference maps and included in the refinement with isotropic temperature factors. For all the other atoms anisotropic temperature factors were introduced. After several cycles the refinement converged to a final value of $R = 0.052^{11}$. Final atomic coordinates are given in Table V. The sum of the three nitrogen bond angles is 320.4° . The pyrroline ring adopts the envelope conformation with N(4) 0.18 Å out of plane of the other four atoms.

C. Preparative Hydrolyses of Parent Compounds. Hydrolysis of Sodium Penem-3-carboxylate (1a). To a solution of **1a** (38.6 mg, 0.2 mmol) in H_2O (2 mL), aqueous NaOH (2 mL, 0.2 mmol) was added and the solution left for 2 days at room temperature under nitrogen. Lyophilization under high vacuum afforded a yellow noncrystalline solid **4a**. For characterization it was suspended in dry dimethyl sulfoxide (0.3 mL), and *p*-nitrobenzyl bromide (86 mg, 0.4 mmol) was added. The mixture was stirred at room temperature for 3 h. Addition of AcOEt (10 mL) and toluene (20 mL), subsequent washing with aqueous 10% Na_2CO_3 solution (10 mL) and water (3×30 mL), drying of the organic layer over Na_2SO_4 , and evaporation of the solvent afforded a yellow noncrystalline solid (82 mg). It was purified by preparative thin layer chromatography on three Merck silica gel plates (20×20 cm) with toluene-AcOEt (1:1). Pure crystalline **4d** (29 mg, 31%) was eluted with AcOEt: mp 103–107 °C. R_f 0.40 (toluene-AcOEt 1:1); UV (EtOH) λ_{max} 263 nm (ϵ 19 000); IR (CH_2Cl_2) 1735, 1605, 1525, 1350 cm^{-1} ; NMR ($CHCl_3$) δ 2.7–3.5 (m, 2), 4.22 (m, 2), 5.25 (s, 2), 5.40 (s, 2), 6.20 (m, 1), 7.55 (m, 4), 8.20 (m, 4); mass, M^+ 459. Anal. Calcd for $C_{20}H_{17}N_3O_5S$ (459.44): C, 52.29; H, 3.73; N, 9.15; S, 6.98. Found: C, 52.57; H, 3.70; N, 9.15; S, 6.30.

Hydrolysis of Sodium 1-Carbapen-2-em-3-carboxylate (2a). To a solution of **2a** (crude reaction mixture described in section A, from 0.2 mmol of **2b**) aqueous NaOH (0.1 N, 2 mL, 0.2 mmol) was added at 0 °C and the reaction mixture stirred at 0 °C for 30 min. It was partly evaporated in vacuo to a volume of 2.5 mL and then lyophilized under high vacuum, affording **5a** (52 mg) as a noncrystalline yellow solid. For characterization it was suspended in dry dimethyl sulfoxide (0.3 mL) and *p*-nitrobenzyl bromide (108 mg, 0.5 mmol) was added. The mixture was

stirred overnight at room temperature. Addition of AcOEt (5 mL) and toluene (5 mL), washing with aqueous 10% Na_2CO_3 solution (10 mL) followed by water (2×20 mL), drying of the organic layer over Na_2SO_4 , and evaporation of the solvent afforded a yellow noncrystalline solid (88 mg). It was purified by preparative thin layer chromatography on three Merck silica gel plates (20×20 cm) with toluene-AcOEt (2:1). Pure crystalline **5d** (21 mg, 24%) was eluted with AcOEt: mp 95–97 °C (AcOEt-EtOEt); R_f 0.23 (toluene-AcOEt 1:1); UV (EtOH) λ_{max} 266 nm (ϵ 19 300); IR (CH_2Cl_2) 1735, 1605, 1525, 1350 cm^{-1} ; NMR ($CDCl_3$) δ 1.64 (m, 1, H-4'); 2.32 (m, 1, H-4), 2.64 (dd, 1, $J = 16, 8$ Hz, H-6'), 2.83 (m, 1, H-3'), 2.99 (m, 1, H-3), 3.01 (dd, 1, $J = 6, 16$ Hz, H-6), 4.66 (m, 1, H-5), 5.25 (s, 2), 5.40 (AB q, 2), 7.53 (d, 2, $J = 9$ Hz), 7.58 (d, 2, $J = 9$ Hz), 8.21 (d, 2, $J = 9$ Hz), 8.23 (d, 2, $J = 9$ Hz); mass, M^+ 441. Anal. Calcd for $C_{21}H_{19}N_3O_5$ (441.40): C, 57.15; H, 4.34; N, 9.52; O, 29.00. Found: C, 57.46; H, 4.40; N, 9.47; O, 28.90.

Hydrolysis of Sodium 1-Carbapen-1-em-3-carboxylate (3a). To a solution of **3a** (41.8 mg, ~ 0.2 mmol) in water (8 mL), aqueous NaOH (0.1 N, 2 mL, 0.2 mmol) was added and the mixture kept for 20 h at room temperature under nitrogen. Lyophilization of the reaction mixture afforded **6a** (55 mg) as a noncrystalline solid. It was suspended in dry dimethyl sulfoxide (0.3 mL) and stirred under nitrogen with *p*-nitrobenzyl bromide (151.2 mg, 0.7 mmol) and potassium *tert*-butoxide (22.4 mg, 0.2 mmol) at 40 °C for 4 h. Addition of toluene (14 mL), subsequent washing with an aqueous solution of Na_2CO_3 (10%, 5 mL) and water (3×15 mL), drying of the organic layer with Na_2SO_4 , and evaporation of the solvent afforded a noncrystalline solid (114 mg). It was purified by preparative thin layer chromatography on five Merck silica gel plates (20×20 cm) with toluene-AcOEt (2:1). Pure crystalline **6d** was eluted with AcOEt: mp 128–131 °C; R_f 0.42 (toluene-AcOEt 1:1); UV (EtOH) λ_{max} 263 nm (ϵ 28 000); IR (CH_2Cl_2) 1735, 1605, 1525, 1350 cm^{-1} ; NMR ($CDCl_3$) δ 2.65 (m, 2, H-6), 4.14 (s, 2), 4.44 (m, 2, H-2 and H-5), 5.15 (s, 2), 5.18 (s, 2), 5.93 (m, 2, H-3 and H-4), 7.45 (m, 6), 8.15 (m, 6); mass, $M - 2$ (dehydrogenation to pyrrole) 574. Anal. Calcd for $C_{28}H_{24}N_4O_{10}$ (576.53): C, 58.33; H, 4.20; N, 9.72. Found: C, 58.42; H, 4.20; N, 9.73.

D. Kinetic Measurements. Preparation of Deuterated Buffer Solution, pD 7.4. Biological buffer solution (pH 7.4,⁹ 5 mL) was lyophilized under high vacuum. The residue was repeatedly lyophilized with D_2O and then the volume adjusted to 5 mL with D_2O .

Determination of the Hydrolysis Rate of 3a by 360-MHz NMR Spectroscopy. A solution containing **3a** (1.75 mg, ~ 10 μ mol) and *tert*-butyl alcohol (0.33 mg, internal standard) in 453 μ L of deuterated buffer solution (pD 7.4) was kept in a NMR tube under nitrogen at 37 °C. At appropriate time intervals the tube was shaken and the spectrum recorded (~ 250 scans). From the integral ratios between the H-5 (δ 4.95 ppm) and the *t*-Bu resonances (δ 1.20 ppm) the half-life was determined. Prolonged hydrolysis (21 days at 37 °C) provided a single product. The NMR was consistent with **6a**: δ 2.57 (dd, 1, $J = 7, 16.5$ Hz, H-6), 2.65 (dd, 1, $J = 6, 16.5$ Hz, H-6'), 4.82 (m, 1, H-5), 4.85 (m, 1, H-2), 5.89 (broad d, 1, $J = 6$ Hz, H-3), 5.97 (broad d, 1, $J = 6$ Hz, H-4).

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Supplementary Material Available: Bond lengths, bond angles, and torsion angles between nonhydrogen atoms for **1b**, **2b**, and **3b** plus thermal parameters (6 pages). Ordering information is given on any current masthead page.