

- Schönberg, B. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).
- (3) H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, ref 2b, Abstract 228.
- (4) Personal communication from Dr. E. Walton.
- (5) The XAD-2 resin (obtained from the Rohm & Haas Co.) is a polystyrene resin which has a strong affinity for compounds containing aromatic moieties when the chromatographic separation is carried out using water as solvent.
- (6) The reverse-phase HPLC analysis of the reaction mixture was performed using a Waters Associates high pressure liquid chromatograph equipped with a 2.5-mm i.d. X 61 cm Bondapak C₁₈/Corosil column. Using 10% THF-H₂O as solvent at 1.0-mL/min flow rate, sodium *N*-phenoxyacetylthienamycin and sodium descysteaminythienamycin showed retention times of 9 and 3 min, respectively.
- (7) High voltage electrophoresis was also used to analyze the reaction mixture. In a typical electrophoretic separation (0.05 M, pH 7.0, sodium phosphate buffer at 2 kv for 20 min on Whatman chromatography paper, followed by bioautographic visualization), sodium *N*-phenoxyacetylthienamycin and sodium descysteaminythienamycin showed mobilities of 5 and 8 cm, respectively, toward the anode.
- (8) The H₄ protons of **4** appeared as two doublets in the 60-MHz NMR spectrum, and as two triplets in the 100-MHz spectrum. Since the outer peaks of the AB pattern could not be observed in the 60- and 100-MHz spectra, the assignment of the chemical shifts of the H_{4α} and H_{4β} protons remain uncertain: K. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", Wiley, New York, 1967, p 130.

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Total Synthesis of Thienamycin Analogues. 1. Synthesis of the Thienamycin Nucleus and *dl*-Descysteaminythienamycin

Sir:

Thienamycin (**16**), a novel β -lactam antibiotic isolated from *Streptomyces cattleya*, is an unusually potent antibiotic.¹ It has three structural features not found in the classical β -lactam antibiotics, the penicillins and cephalosporins:² (1) an α -hydroxyethyl side chain instead of a β -amido side chain at C-6, (2) an unusual cysteamine side chain at position 2, and (3) a highly strained nucleus consisting of an unsaturated five-membered ring fused to a β -lactam in which a methylene replaces the sulfur at position 1, found in conventional β -lactam antibiotics.

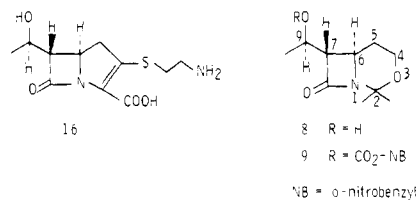
Introduction of the hydroxyethyl side chain at the 6(7) position of a penicillin (cephalosporin)³ or of a cysteamine side chain at position 3 of a cephalosporin⁴ did not increase the activity of these nuclei, leading us to believe that the nucleus of thienamycin, 1-carba-2-penam-3-carboxylic acid, may have high antibiotic activity and may be a major contributor to the unusual antibiotic activity of thienamycin.

We describe below the synthesis of sodium 1-carba-2-penam-3-carboxylate (**7**) and its (*R*)-6 α -hydroxyethyl ana-

logue (**15**) and report on the antibiotic activity of **7**.⁵ Condensation of 4-(2-acetoxyethyl)-azetidin-2-one (**1**)⁶ with 2 equiv of *o*-nitrobenzyl glyoxalate, (C₆H₆, Δ , Dean-Stark, CaH₂, 3 h) gave the hydroxy acetate **2** (70%) after silica gel chromatography (50% EtOAc-C₆H₆): IR⁷ 3300 (OH), 1760 (β -lactam), 1740 (ester), 1530 (NO₂); NMR⁷ 7.5-8.4 (m, *o*-C₆H₄NO₂), 5.66 (s, CH₂Ar), 5.5 (d, -CHOH), 4.2 (2t, CH₂OAc), 3.95 (m, C-4 H), 3.15 (q, *J* = 5, *J* = 15 Hz, C-3 α H), 2.65 (q, *J* = 3, *J* = 15 Hz, C-3 β H), 2.05 (s, CH₃C), 1.95 (m, CH₂CH₂O). Hydroxy acetate **2** gave the unstable chloro compound **3** (SOCl₂, pyridine, THF, -20 to 25 °C, 25 min) which without purification was converted to the ylide-acetate **4** (Ph₃P, DMF, 1 hr, 25 °C) in 82% yield after silica gel chromatography (EtOAc): IR 1740 (β -lactam, ester), 1620 (benzyl ester), 1525 (NO₂); NMR 7.2-8.2 (m, aromatic H), 5.1-5.8 (m, CH₂Ar), 4.12 (q, CH₂OAc), 1.96 (s, CH₃C=O).

The negative charge on the ylide carbon decreases the bond energy of both the β -lactam and ester carbonyl to which it is adjacent; this is reflected in the shift of both carbonyl absorptions to longer wavelengths (1740 and 1620 cm⁻¹ in **4** vs. 1760 and 1740 cm⁻¹ in **2**). Hydrolysis of **4** with 1.2 equiv of NaOMe in MeOH (25 °C, 1 h), followed by chromatography on silica gel (5% MeOH, EtOAc), gave alcohol **5** (86%; IR (3600 (OH), 1740 (β -lactam), 1630 (benzyl ester), 1530 (NO₂)) with no evidence of ester exchange or hydrolysis of the azetidinone, both functions being protected against nucleophilic attack by the presence of the negative charge on the adjoining ylide carbon. Oxidation of the ylide-alcohol **5** (Me₂SO, Ac₂O, 25 °C, 3.5 h) gave the corresponding aldehyde which spontaneously cyclized to the carbapenam **6** (30%, after preparative TLC on silica gel): IR 1772 (β -lactam), 1722 (ester), 1660 (C=C), 1530 (NO₂); NMR 7.3-8.5 (m, -O-C₆H₄NO₂), 6.61 (t, C-2 H), 5.73 (q, AB, CH₂Ar), 4.35 (m, *J* = 3, *J* = 5, *J* = 8 Hz, C-3 H), 3.58 (q, *J* = 5, *J* = 14 Hz, C-6 α H), 2.99 (q, *J* = 3, *J* = 14 Hz, C-6 β H), 2.96 (t, C-1 H); UV $\lambda_{\text{max}}^{\text{EtOH}}$ 265 nm (ϵ 9200); mass spectrum *m/e* 288. Photolysis of **6** (degassed dioxane-water, 1 equiv of NaHCO₃, 350 nm, Rayonet reactor, 25 °C, cold finger cooling, 55 min) gave the desired carbapenam sodium salt **7**: 19%;⁸ UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 262 nm (extinguishable by addition of NH₂OH).

The antibiotic activity of **7**, shown in Table I, is compared with those of thienamycin and ampicillin. The nucleus of thienamycin is itself a powerful antibiotic and contributes a major factor toward the remarkable activity of **16**; however



it is susceptible to β -lactamases as shown by its low activity against penicillinase-producing strains.

The above synthesis can be modified to prepare analogues of thienamycin; this is demonstrated below by the synthesis of descysteaminythienamycin (**15**) which can also be obtained

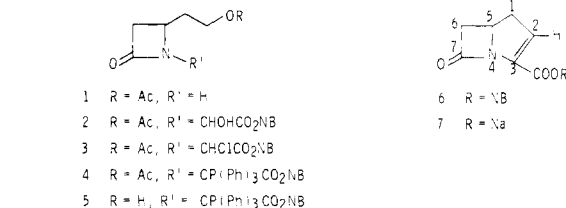
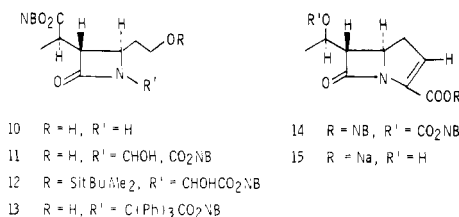


Table 1. Inhibitory Zone Diameters (Millimeters) vs. Penicillin-Sensitive and Resistant Bacterial Strains

compd	disc content, μg (nmol)	<i>S. aureus</i>		<i>E. coli</i>		<i>Enterobacter cloacae</i>	
		MB2985	MB2314	MB2482	MB2964	MB2647	MB2646
ampicillin	10 (28)	33.5	13	20.3	0	18	0
thienamycin	6.3 (23)	38.5	38.5	25	25.5	22.5	22
7 ^a	8.2 (54)	20.5	0	20	0	21	16.5

^a 54 nmol of racemic **7** corresponds to 27 nmol of active **7**.

from thienamycin as shown in an accompanying publication.⁵



8-Oxo-2,2-dimethyl-7 α -(1'-hydroxyethyl)-3-oxa-1-aza-bicyclo[4.2.0]octane (**8**)⁶ was converted to its *o*-nitrobenzyl-carbonate **9** (C₆H₄NO₂CH₂O₂CCl, 2 equiv of Me₂NC₅H₄N, 2 equiv of CH₂Cl₂, 0 °C \rightarrow room temperature, 3 h) and the two isomers at C-9 were separated by HPLC (silica gel, 30% EtOAc-C₆H₁₂). The acetonide function of the 9*R* isomer of **9** was hydrolyzed (TFA, H₂O, room temperature, 12 min) to give the alcohol **10** (85%; IR 3430 (OH and NH), 1750 (β -lactam and carbonate), 1530 (NO₂); NMR 7.3–8.3 (m, *O*-C₆H₄NO₂), 6.53 (s, NH), 5.6 (s, CH₂Ar), 5.2 (2 q, CH₃CH), 3.8 (t and m, CH₂OH and C-4 H), 3.1 (q, *J* = 2, *J* = 9 Hz, C-3 H), 2.3 (s, OH), 1.93 (q, CH₂CH₂OH), 1.48 (d, *J* = 6 Hz, CH₃-) which was condensed with *o*-nitrobenzyl glyoxylate to give the diol **11** (70%). The primary alcohol of **11** was protected as the *tert*-butyl dimethylsilyl ether (*t*-BuMe₂SiCl, DMF, Et₃N) and the product **12** (90% yield) was converted to the ylide as described for **2**. The *tert*-butyldimethylsilyl ether was then hydrolyzed (0.5% concentrated HCl, DMF) to give the ylide-alcohol **13** (62% from **12**). Oxidative cyclization (Me₂SO, Ac₂O) gave the protected *dl*-descysteaminythienamycin **14**: IR 1780 (β -lactam), 1742 (carbonate), 1722 (ester); NMR 7.3–8.3 (m, *O*-C₆H₄NO₂), 6.6 (t, C-2 H), 5.7 (AB q, ArCH₂ of ester), 5.6 (s, ArCH₂ of carbonate), 5.3 (m, CH₃CH), 4.36 (sextet, *J* = 8, *J* = 2 Hz, C-5 H), 3.46 (q, *J* = 2, *J* = 8 Hz, C-6 H), 2.96 (sextet, C-1 H), 1.6 (d, *J* = 6 Hz, CH₃-); 28% (accompanied by 50% methyl thiomethyl ether of **13**). Photolysis of **14** (dioxane, 50% H₂O, pH 7 phosphate buffer 0.5 M, 5%) gave *dl*-descysteaminythienamycin (**15**) which after purification on a XAD-2 column⁵ was identical by NMR and UV with the product obtained from thienamycin.⁵

The use of this synthesis to prepare other analogues of thienamycin will be the subject of future communications.

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References and Notes

- (1) Papers presented at the Sixteenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., Oct 1976: (a) "Thienamycin, A New β -Lactam Antibiotic. I. Discovery and Isolation" by J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff; (b) "Thienamycin, A New β -Lactam Antibiotic. II. In Vitro and In Vivo Evaluation" by H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum.
- (2) G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).
- (3) F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.*, **42**, 2960 (1977).
- (4) L. D. Cama, unpublished results, MSDRL, Rahway.
- (5) D. H. Shih and B. G. Christensen describe the antibiotic activity of **15**: *J. Am. Chem. Soc.*, preceding paper in this issue.
- (6) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).
- (7) IR Spectra were run on thin film and are reported in cm⁻¹; NMR spectra were run in CDCl₃ on a Varian T-60 instrument and are reported in δ units.
- (8) Compound **7** could not be lyophilized without considerable decomposition. IR and NMR spectra of **7** are therefore not available; its presence in aqueous solution is inferred from its UV maxima at 262 nm (NH₂OH extinguisable) similar to descysteaminythienamycin. Reductive cleavage of benzyl or

p-nitrobenzyl used as protecting groups gave **7** in very low yield. The yield and antibiotic activity of **7** is calculated using an assumed ϵ 7800 similar to descysteaminythienamycin.

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Nitrogen Fixation via Photoenhanced Reduction on p-GaP Electrodes

Sir:

The fixation of N₂ under mild ambient conditions has been an extremely important and long-standing objective of much international research. A system is reported here which produces N₂ fixation at room temperature and atmospheric pressure by a photoenhanced reduction process. The system is a photoelectrochemical cell which contains a p-GaP cathode and an aluminum metal anode immersed in a nonaqueous electrolyte of titanium tetraisopropoxide and AlCl₃ dissolved in glyme (1,2-dimethoxyethane). When N₂ is passed through the electrolyte and the p-GaP electrode is illuminated with band-gap light, the N₂ is reduced and is recovered as NH₃; aluminum is consumed in the process and acts as the reducing agent. Although the reduction of N₂ to NH₃ with aluminum is thermodynamically favored ($\Delta G < 0$), the reaction does not proceed in the cell in the dark. The activation energy for the process is provided by light absorbed in the p-GaP electrode; hence, this system is an example of photocatalysis in a photoelectrochemical cell. The cell has been successfully operated in both flow and static modes; in the former, N₂ is continuously bubbled through the electrolyte. Experiments using ¹⁵N₂ have also been carried out and ¹⁵NH₃ has been identified from Fourier transform IR spectra.

The cell and electrolyte used in this work are closely related to those used by Van Tamelen and co-workers¹⁻³ to demonstrate normal electrolytic fixation of N₂. In those previous experiments, an external voltage source was used with either two Pt electrodes¹ or with an aluminum anode and a Nichrome cathode² to fix molecular nitrogen. In the present system, no external voltage source is required to achieve N₂ fixation; the activation energy for the reaction is provided by light alone.

The flow experiments were conducted in a closed quartz cell by bubbling high purity (99.999%) nitrogen gas through 80 mL of glyme containing 40 mmol of titanium isopropoxide and 60 mmol of AlCl₃; the effluent N₂ gas was then passed through a 0.2 N H₂SO₄ trap before exiting to the atmosphere. The p-GaP cathode was fabricated from a 1-mm-thick Zn-doped single-crystal wafer (<111> orientation) with an area of 1 cm², a carrier density of 5×10^{17} cm⁻³, and a conductivity of 5.4 Ω^{-1} cm⁻¹. The crystal was polished with alumina powder and etched in a 3:1:1 H₂SO₄-H₂O₂-H₂O solution at 60 °C for 10 min; a 3000-Å film of a 1% Zn in gold alloy was then evaporated on the Ga face (111), and this was followed by heat treatment in 90% Ar-10% H₂ at 600 °C for 10 min to produce an ohmic contact to the crystal.

The anode consisted of ultra-high-purity aluminum wire. A low-impedance Keithley K616 ammeter or a PAR 179 coulometer was connected between the electrodes to measure current or total charge flow. The N₂ flow rate was ~ 14 cm³/min, and the light intensity was ~ 100 mW/cm² of simulated sunlight from a 150-W xenon lamp. A typical run lasted 24 h.

Reduced nitrogen yields were based on analyses of both the 0.2N H₂SO₄ trap and the residual electrolyte. The acid trap was analyzed directly for NH₄⁺, while the residual electrolyte was first digested in sulfuric acid and then treated with 8 N