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(3) H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, ref 2b, Abstract 228.
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(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. × 61 cm Bondapak C_{18}/Corosil column. Using 10% THF–H_2O as solvent at 1.0-mL/min flow rate, sodium *N*-phenoxyacetylthienamycin and sodium descysteaminylthienamycin 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 descysteaminylthienamycin showed mobilities of 5 and 8 cm, respectively, toward the anode.
(8) The H_4 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 $H_{4\alpha}$ and $H_{4\beta}$ 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*-Descysteaminylthienamycin

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.

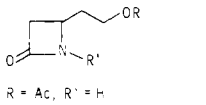
Introduction of the hydroxyethyl side chain at the 6(7) position of a penicillin (cephalosporin)[3] or of a cysteamine side chain at position 3 of a cephalosporin[4] did not increase the activity of these nuclei, leading us to believe that the nucleus of thienamycin, 1-carba-2-penem-3-carboxylic acid, 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-penem-3-carboxylate (**7**) and its (*R*)-6α-hydroxyethyl analogue (**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, (C_6H_6, Δ, Dean-Stark, CaH_2, 3 h) gave the hydroxy acetate **2** (70%) after silica gel chromatography (50% EtOAc–C_6H_6): IR[7] 3300 (OH), 1760 (β-lactam), 1740 (ester), 1530 (NO_2); NMR[7] 7.5–8.4 (m, *o*-$C_6H_4NO_2$), 5.66 (s, CH_2Ar), 5.5 (d, -C*H*OH), 4.2 (2t, CH_2OAc), 3.95 (m, C-4 H), 3.15 (q, J = 5, J = 15 Hz, C-3α H), 2.65 (q, J = 3, J = 15 Hz, C-3β H), 2.05 (s, CH_3C), 1.95 (m, CH_2CH_2O). Hydroxy acetate **2** gave the unstable chloro compound **3** ($SOCl_2$, pyridine, THF, −20 to 25 °C, 25 min) which without purification was converted to the ylide-acetate **4** (Ph_3P, DMF, 1 hr, 25 °C) in 82% yield after silica gel chromatography (EtOAc): IR 1740 (β-lactam, ester), 1620 (benzyl ester), 1525 (NO_2); NMR 7.2–8.2 (m, aromatic H), 5.1–5.8 (m, CH_2Ar), 4.12 (q, CH_2OAc), 1.96 (s, CH_3C=O).

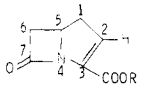
The negative charge on the ylide carbon decreases the bond energy of both the β-lactam and ester carbonyl to which it is adjacent; this is reflected in the shift of both carbonyl absorptions to longer wavelengths (1740 and 1620 cm^{-1} in **4** vs. 1760 and 1740 cm^{-1} in **2**). Hydrolysis of **4** 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 (NO_2)) 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** (Me_2SO, Ac_2O, 25 °C, 3.5 h) gave the corresponding aldehyde which spontaneously cyclized to the carbapenem **6** (30%, after preparative TLC on silica gel): IR 1772 (β-lactam), 1722 (ester), 1660 (C=C), 1530 (NO_2); NMR 7.3–8.5 (m, -*O*-$C_6H_4NO_2$), 6.61 (t, C-2 H), 5.73 (q, AB, CH_2Ar), 4.35 (m, J = 3, J = 5, J = 8 Hz, C-3 H), 3.58 (q, J = 5, J = 14 Hz, C-6α H), 2.99 (q, J = 3, J = 14 Hz, C-6β H), 2.96 (t, C-1 H); UV λ_{max}^{EtOH} 265 nm ε 9200); mass spectrum *m/e* 288. Photolysis of **6** (degassed dioxane–water, 1 equiv of $NAHCO_3$, 350 nm, Rayonet reactor, 25 °C, cold finger cooling, 55 min) gave the desired carbapenem sodium salt **7**: 19%;[8] UV $\lambda_{max}^{H_2O}$ 262 nm (extinguishable by addition of NH_2OH).

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.

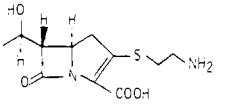
The above synthesis can be modified to prepare analogues of thienamycin; this is demonstrated below by the synthesis of descysteaminylthienamycin (**15**) which can also be obtained



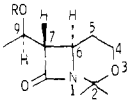
1 R = Ac, R' = H
2 R = Ac, R' = CHOHCO$_2$NB
3 R = Ac, R' = CHClCO$_2$NB
4 R = Ac, R' = CPh$_3$CO$_2$NB
5 R = H, R' = CPh$_3$CO$_2$NB



6 R = NB
7 R = Na



16



8 R = H
9 R = CO$_2$-NB

NB = *o*-nitrobenzyl

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

compd	disc content, μg (nmol)	*S. aureus*		*E. coli*		Enterobacter clocae	
		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**.

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from thienamycin as shown in an accompanying publication.[5]

10 R = H, R' = H
11 R = H, R' = CHOH, CO_2NB
12 R = SiBuMe$_2$, R' = CHOHCO_2NB
13 R = H, R' = C(Ph)$_3$ CO_2NB

14 R = NB, R' = CO_2NB
15 R = Na, R' = H

8-Oxo-2,2-dimethyl-7α-(1'-hydroxyethyl)-3-oxa-1-azabicyclo[4.2.0]octane (**8**)[6] was converted to its *o*-nitrobenzylcarbonate **9** ($C_6H_4NO_2CH_2O_2CCl$, 2 equiv of $Me_2NC_5H_4N$, 2 equiv of CH_2Cl_2, 0 °C → room temperature, 3 h) and the two isomers at C-9 were separated by HPLC (silica gel, 30% EtOAc-C_6H_{12}). The acetonide function of the 9*R* isomer of **9** was hydrolyzed (TFA, H_2O, room temperature, 12 min) to give the alcohol **10** (85%; IR 3430 (OH and NH), 1750 (β-lactam and carbonate), 1530 (NO_2); NMR 7.3-8.3 (m, *O*-$C_6H_4NO_2$), 6.53 (s, NH), 5.6 (s, CH_2Ar), 5.2 (2 q, CH_3CH), 3.8 (t and m, CH_2OH and C-4 H), 3.1 (q, J = 2, J = 9 Hz, C-3 H), 2.3 (s, OH), 1.93 (q, CH_2CH_2OH), 1.48 (d, J = 6 Hz, CH_3-)) 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*-$BuMe_2SiCl$, DMF, Et_3N) 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 (Me_2SO, Ac_2O) gave the protected *dl*-descysteaminylthienamycin **14:** IR 1780 (β-lactam), 1742 (carbonate), 1722 (ester); NMR 7.3-8.3 (m, *O*-$C_6H_4NO_2$), 6.6 (t, C-2 H), 5.7 (AB q, $ArCH_2$ of ester), 5.6 (s, $ArCH_2$ of carbonate), 5.3 (m, CH_3CH), 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, CH_3-); 28% (accompanied by 50% methyl thiomethyl ether of **13**). Photolysis of **14** (dioxane, 50% H_2O, pH 7 phosphate buffer 0.5 M, 5%) gave *dl*-descysteaminylthienamycin (**15**) which after purification on a XAD-2 column[5] 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.

Acknowledgments. We thank Dr. Byron H. Arison and Mr. Herman Flynn for 300-MHz proton NMR spectra, Mr. Jack Smith for mass spectra, and Ms. Jean S. Kahan for the in vitro antibacterial assay.

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.
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(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 $CDCl_3$ 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 (NH_2OH extinguishable) similar to descysteaminylthienamycin. 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 descysteaminylthienamycin.

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Nitrogen Fixation via Photoenhanced Reduction on p-GaP Electrodes

Sir:

The fixation of N_2 under mild ambient conditions has been an extremely important and long-standing objective of much international research. A system is reported here which produces N_2 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 $AlCl_3$ dissolved in glyme (1,2-dimethoxyethane). When N_2 is passed through the electrolyte and the p-Gap electrode is illuminated with band-gap light, the N_2 is reduced and is recovered as NH_3; aluminum is consumed in the process and acts as the reducing agent. Although the reduction of N_2 to NH_3 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, N_2 is continuously bubbled through the electrolyte. Experiments using $^{15}N_2$ have also been carried out and $^{15}NH_3$ 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-workers[1-3] to demonstrate normal electrolytic fixation of N_2. In those previous experiments, an external voltage source was used with either two Pt electrodes[1] or with an aluminum anode and a Nichrome cathode[2] to fix molecular nitrogen. In the present system, no external voltage source is required to achieve N_2 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 $AlCl_3$; the effluent N_2 gas was then passed through a 0.2 N H_2SO_4 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 cm^2, 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 H_2SO_4-H_2O_2-H_2O 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% H_2 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 N_2 flow rate was ~14 cm^3/min, and the light intensity was ~100 mW/cm^2 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 H_2SO_4 trap and the residual electrolyte. The acid trap was analyzed directly for NH_4^+, while the residual electrolyte was first digested in sulfuric acid and then treated with 8 N

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