Johnson, J. D. Rush, and A. Simopoulos, *Biochem. J.*, **151**, 75 (1975).
(13) R. Cammack, *Biochem. Soc. Trans.*, **3**, 482 (1975).
(14) R. E. Anderson, G. Anger, L. Petersson, A. Ehrenberg, R. Cammack, D. O. Hall, R. Mullinger, and K. K. Rao, *Biochim. Biophys. Acta*, **376**, 63 (1975).
(15) W. D. Phillips, C. C. McDonald, N. A. Stombaugh, and W. H. Orme-Johnson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 140 (1974).
(16) C. L. Thompson, C. E. Johnson, D. P. E. Dickson, R. Cammack, D. O. Hall, U. Weser, and K. K. Rao, *Biochem. J.*, **139**, 97 (1974).
(17) δ (mm/s), 4.2 K $[Fe_4S_4(SPh)_4]^{2-}$, 0.35; $[Fe_4S_4(SCH_2Ph)_4]^{2-}$, 0.34: R. B. Frankel, B. A. Averill, and R. H. Holm, *J. Phys. (Paris)*, **35**, C6-107 (1974).
(18) D. P. E. Dickson, C. E. Johnson, C. L. Thompson, R. Cammack, M. C. W. Evans, D. O. Hall, K. K. Rao, and U. Weser, *J. Phys. (Paris)*, **35**, C6-343 (1974); R. Cammack, D. P. E. Dickson, and C. E. Johnson in "Iron-Sulfur Proteins", Vol. III, W. Lovenberg, Ed., Academic Press, New York, N.Y., 1977, Chapter 8.
(19) R. H. Holm, B. A. Averill, T. Herskovitz, R. B. Frankel, H. B. Gray, O. Siiman, and F. J. Grunthaner, *J. Am. Chem. Soc.*, **96**, 2644 (1974).
(20) Visiting Scholar, 1975–1976; Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia.

R. W. Lane, A. G. Wedd,[20] W. O. Gillum
E. J. Laskowski, R. H. Holm*
Department of Chemistry, Stanford University
Stanford, California 94305

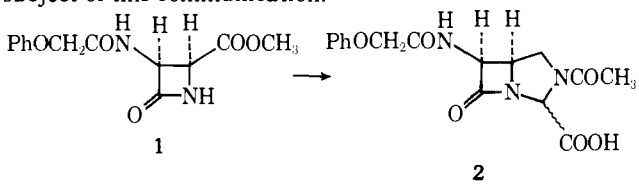
R. B. Frankel,* G. C. Papaefthymiou
Francis Bitter National Magnet Laboratory
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received November 15, 1976

Nuclear Analogues of β-Lactam Antibiotics. 1. The Total Synthesis of a 7-Oxo-1,3-diazabicyclo[3.2.0]heptane-2-carboxylic Acid via a Versatile Monocyclic β-Lactam Intermediate

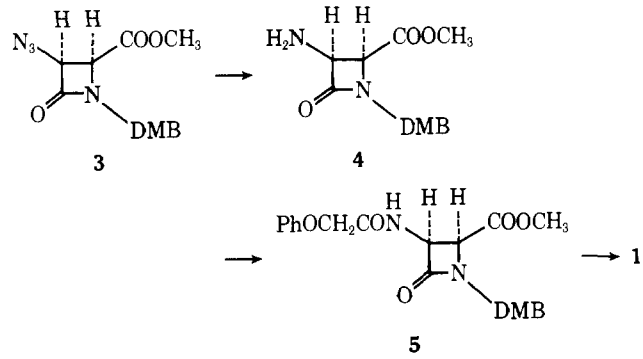
Sir:

The search for more effective antibacterial agents has led to the partial synthesis of a vast number of penicillin and cephalosporin derivatives which differ primarily in the nature of the acylamino substituent at C-6(7) and, for cephalosporins, the substituent at C-3. Analogous structures with more profound modifications, particularly new ring systems, are of considerable interest because they have the potential of offering improved therapy and may be useful in determining the mechanism of action of the β-lactam class of antibiotics. Only a limited number of such nuclear analogues are known because the preparation of each requires either extensive degradation and resynthesis starting from the natural products[1] or a multistep total synthesis.[2] We have developed a versatile monocyclic β-lactam intermediate[3] which allows for the synthesis of a wide variety of biologically active nuclear analogues.[4] The stereoselective synthesis of this key intermediate (**1**) and its subsequent conversion to a bicyclic structure (**2**) which incorporates some important features of the penicillins is the subject of this communication.



1 **2**

Addition of the mixed anhydride of azidoacetic acid and trifluoracetic anhydride[5] to a mixture of triethylamine and the imine formed from 2,4-dimethoxybenzylamine and methyl glyoxylate afforded *cis*-azido-β-lactam **3**[6] (58%; mp 82–84 °C; λ_{max}^{Nujol} 4.72 (azide) and 5.62 μ (β-lactam CO); $\delta_{Me_4Si}^{CDCl_3}$ 4.08 and 4.68 (d, J = 5.5 Hz, β-lactam C–H's)) with none of the trans isomer detected. The conversion of azide **3** into



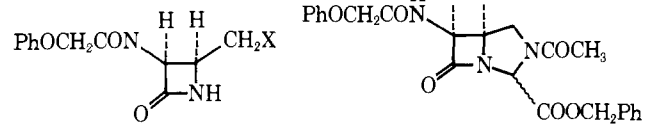
3 **4** **5**

phenoxyacetylamide **1** was accomplished in the following manner.

Catalytic hydrogenation of azide **3** (10% Pd–C, EtOH, 60 psi, 40 °C, 2 h) afforded the amine **4** as a clear gum which was acylated with phenoxyacetyl chloride[7] (Et_3N, CH_2Cl_2, 0 °C, 1 h) to give amide **5** in 84% yield for the two steps. The β-lactam nitrogen was conveniently deblocked by oxidative cleavage with buffered potassium persulfate[8] (4 equiv of $K_2S_2O_8$, 2 equiv of $Na_2HPO_4 \cdot 7H_2O$, 40% aqueous CH_3CN, reflux, 1 h) to afford phenoxyacetylamide **1** [(69%; mp 140–141 °C; λ_{max}^{Nujol} 5.63, 5.73, and 6.00 μ; $\delta_{Me_4Si}^{Me_2SO\text{-}d_6}$ $CDCl_3$ 3.59 (s, $COOCH_3$), 4.35 (d, J = 6 Hz, C-2H), 4.48 (s, $PhOCH_2CO$–), 5.33 and 5.50 ((d, J = 6 Hz, C-3H) also split by C-3 NH (d, J = 10 Hz)); *m/e* 278 (M^+) and 235 ($M^+ - 43$))].

Intermediate **1** is well suited for conversion into a variety of β-lactam antibiotic nuclear analogues which possess structural features believed necessary for good antibacterial activity.[9] The 7-oxo-1,3-diazabicyclo[3.2.0]heptane-2-carboxylic acid system **2**, a penicillin nuclear analogue, was selected as an initital synthetic target.

Selective sodium borohydride reduction[10] of the methyl ester of **1** afforded alcohol **6** (79%; H_2O–THF, 0 °C, 1 h) which was converted into the tosylate derivative (**7**) (79%; *p*-TsCl, pyr, 0 °C). Sodium iodide displacement gave iodide **8** (85%; NaI, acetone, reflux, 6 h) which was subsequently displaced with azide ion to yield azide **9** (75%; NaN_3, DMF, 25 °C, 48 h). Catalytic hydrogenation of **9** (10% Pd–C, EtOH, 25 °C, 2 h) followed by condensation of the resulting amine (**10**) with benzyl glyoxylate ($MgSO_4$, CH_2Cl_2, 25 °C, 2 h) afforded crystalline imine **11** (65%; mp 129–131 °C; λ_{max}^{Nujol} 5.62, 5.69, and 6.01 μ; $\delta_{Me_4Si}^{CDCl_3}$ 3.65 (m, $-CH_2N{=}CH$), 4.05 (m, C-2H), 4.45 (s, OCH_2CO), 5.20 (s, $COOCH_2Ph$), 5.36 and 5.52 (s, J = 5.5 Hz, C-3H coupled to C-2H and CONH), and 8.00 (d, J = 9 Hz, CH_2CONH); *m/e* 395 (M^+), 304, 260, 217). Treatment of **11** with acetyl chloride (CH_2Cl_2, pyr, 0 to 25 °C, 2 h) resulted in acylative cyclization to give benzyl ester **12** (mp 148–150 °C; λ_{max}^{Nujol} 5.57, 5.75, 5.96, and 6.15 μ; $\delta_{Me_4Si}^{CDCl_3}$ 1.93 (s, $COCH_3$), 4.52 (s, $PhOCH_2CO$), 5.15 (s, $COOCH_2Ph$), 5.40 (m, C-6H), and 5.93 (s, C-2H); *m/e* 437 (M^+), 302, 274, 247, 232, 205, 69) in 16–20% yield after purification by either column chromatography or fractional crystallization. ^1H NMR spectral evidence indicated that **12**



6, X = OH
7, X = OTs
8, X = I
9, X = N_3
10, X = NH_2
11, X = N=$CHCO_2CH_2Ph$

12

was a mixture (ca. 3:1) of carboxylate epimers. Quantitative cleavage of the benzyl ester was effected by catalytic hydrogenation (10% Pd-C, EtOAc, 1 atm, 25 °C) to give the desired acid **2** (λ_{max}^{Nujol} 5.56, 5.76, and 5.97 μ) as a mixture of carboxylate epimers which were unstable in aqueous solution ($t_{1/2}$ = 2 h; 37 °C; pH 7.0). Despite its instability acid **2** did exhibit antibacterial activity against selected gram-positive and gram-negative organisms. Growth inhibition of *Bacillus subtilis, Staphylococcus aureus*, and *Shigella paradysenteriae* was observed at concentrations of 10, 100, and 400 μg/mL, respectively.

Acknowledgment. We are grateful to Mr. Donald H. Pitkin for the in vitro microbiological data presented in this paper.

References and Notes

(1) See for instance (a) S. Wolfe, J.-B. Ducep, K.-C. Tin, and S.-L. Lee, *Can. J. Chem.*, **52**, 3996 (1974), and (b) R. B. Woodward, U.S. Patent 3 835 130 (1974).

(2) For example see (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974), and (b) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *ibid.*, **96**, 7584 (1974).

(3) Elaboration of a monocyclic β-lactam into a bicyclic β-lactam structure has proved to be a useful concept as exemplified by ref 1 and 2 above.

(4) The accompanying communication describes the synthesis of another novel fused-ring β-lactam system from a similar monocyclic β-lactam; D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *J. Am. Chem. Soc.*, following paper in this issue. See also J. Finkelstein, K. G. Holden, R. Sneed, and C. D. Perchonock, submitted for publication.

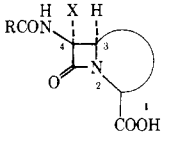
(5) A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 2319 (1973).

(6) Satisfactory spectral data and combustion analysis were obtained for all compounds.

(7) The nitrogen atom can also be protected at this point as a carbamate using such groups as carbobenzyloxy and *tert*-butyloxy.

(8) Simple amides have been oxidatively dealkylated (H. L. Needles and R. E. Whitfield, *J. Org. Chem.*, **29**, 3632 (1964)); however, the use of the dimethoxybenzyl group in this way and its application to β-lactams is new.

(9) These features are illustrated diagramatically in formula i and include: (1)



i

a strained β-lactam resulting from ring fusion, (2) an acylamino function at C-4, (3) cis stereochemistry at C-3,4 (X = H or OCH_3), and (4) a carboxylic acid or its equivalent at C-1.

(10) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963), and P. L. Hall and R. B. Perfetti, *J. Org. Chem.*, **39**, 111 (1974).

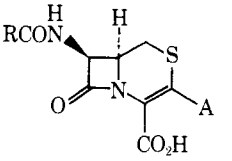
William F. Huffman,* Kenneth G. Holden
Thomas F. Buckley, III, John G. Gleason, L. Wu
Research and Development Division
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

Received October 26, 1976

Nuclear Analogues of β-Lactam Antibiotics. 2. The Total Synthesis of 8-Oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acids[1]

Sir:

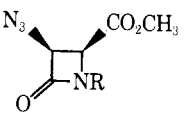
The microorganisms which produce penicillins and Cephalosporin C are capable of producing a limited number of structural modifications; molecules in which the basic heterocyclic ring system is altered are primarily accessible only by total synthesis. We have developed a synthetic approach to such nuclear analogues which allows the stereospecific total synthesis of a number of widely divergent structural types from a single monocyclic β-lactam precursor.[1a,2] In this communication, we report the total synthesis of the *cis*-8-oxo-4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (isocephalosporin[1b]) nucleus (**1**)[3] which illustrates the versatility of our approach.

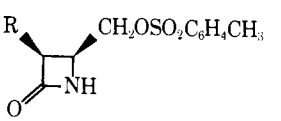


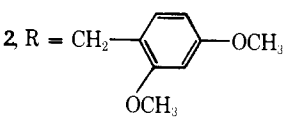
1

The monocyclic *cis*-azetidinone[1a] **2** incorporates both the desired cis stereochemistry as well as the necessary functionalization for subsequent transformation into **1**. The β-lactam nitrogen was deblocked by oxidative cleavage ($K_2S_2O_8$, pH 5-6.5) to afford **3** in high yield.[1a] Selective reduction[4] of the methyl ester with sodium borohydride and tosylation of the resulting alcohol gave *cis*-2-(3-azido-4-oxoazetidenyl)methyl tosylate (**4**). Reduction of the azide (zinc-acetic acid) and coupling of the resulting amine **5** with thienylacetic acid afforded amide **6**: IR (Nujol) ν_{max} 1755 (β-lactam), 1665 cm^{-1} (amide); NMR ($CDCl_3$) δ 8.75 (d, J = 7 Hz, NH), 8.4 (s, β-lactam NH), 6.8-8.0 (m, C_6H_5 + thienyl), 5.1 (dd, J = 4 Hz, 7 Hz, C-3H), 3.8 (m, CH_2-O + C-2H), 3.6 (s, CH_2CO), 2.4 (s, CH_3). Transformation of **6** to the corresponding thiol **9** was achieved by conversion to iodide **7** (sodium iodide, acetone), displacement of the iodide with the sodium salt of trityl mercaptan, and cleavage of the resulting thioether **8** (silver nitrate, methanol).[6]

Alkylation of thiol **9** with benzhydryl β-bromopyruvate[7] afforded the intermediate carbinolamide **10** (IR (film) ν_{max} 1770 (β-lactam), 1750 (ester) and 1650 cm^{-1} (amide)) which on dehydration with thionyl chloride-pyridine gave ester **11** in 14% yield:[8] IR (film) ν_{max} 1760 (β-lactam), 1710 (ester), and 1670 cm^{-1} (amide); NMR ($CDCl_3$) δ 7.2 (m,





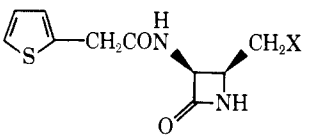


2, R = CH_2-(3,4-$(OCH_3)_2$)

4, R = N_3

5, R = H_2N

3, R = H

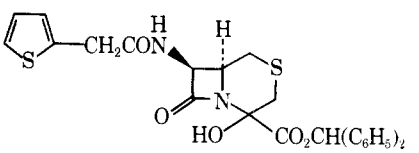


6, X = $OSO_2C_6H_4CH_3$

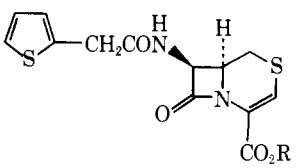
7, X = I

8, X = $SC(C_6H_5)_3$

9, X = SH



10



11, R = $CHPh_2$

12, R = H