Tetrahedron Vol. 39, No 15, pp. 2571 to 2575, 1983
Printed in Great Britain.

0040-4020/83 $3.00 + .00
Pergamon Press Ltd

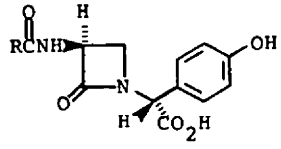
PRACTICAL SYNTHETIC APPROACHES TO INTERMEDIATES FOR THE PREPARATION OF THE NOVEL O-SULFONATED-N-HYDROXY-2-AZETIDINONE ANTIBIOTICS

MARVIN J. MILLER,*[1] ATANU BISWAS and MARK A. KROOK
Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556, U.S.A.

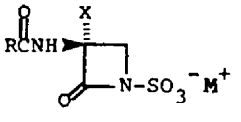
(*Received in UK* 10 *November* 1982)

Abstract—A practical synthesis of intermediates useful for the preparation of a variety of monocyclic β-lactam antibiotics is described. Hydroxaminolysis of N-protected serine esters provided the hydroxamic acids **10**. Acylation followed by cyclization yielded the β-lactams **12**. Solvolytic deacylation gave the parent N-hydroxy-2-azetidinones **7** which can be converted to the N-unsubstituted 2-azetidinones **8** or the novel O-sulfonated antibiotics **3**. The N-unsubstituted-2-azetidinones **8** are also useful for the preparation of the nocardicins and the monobactams.

The recent discovery and structural elucidation of the β-lactamase inhibitor clavulanic acid, the antibiotic penems, and carbapenems, as well as the monocyclic nocardicins **1**, and monobactams **2**,[2] (sulfazecins),[3] has necessitated a reconsideration of the structure-activity relationships of the β-lactam antibiotics. Consequently, related synthetic and enzymatic studies have justifiably received renewed emphasis. In this paper we report a relatively simple and practical synthetic approach to key intermediates for the preparation of monocyclic β-lactams, including the nocardicins, monobactams and the new O-sulfonated N-hydroxy-2-azetidinone antibiotics **3**.

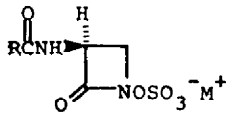


1



2

(X=H, CH_3)



3

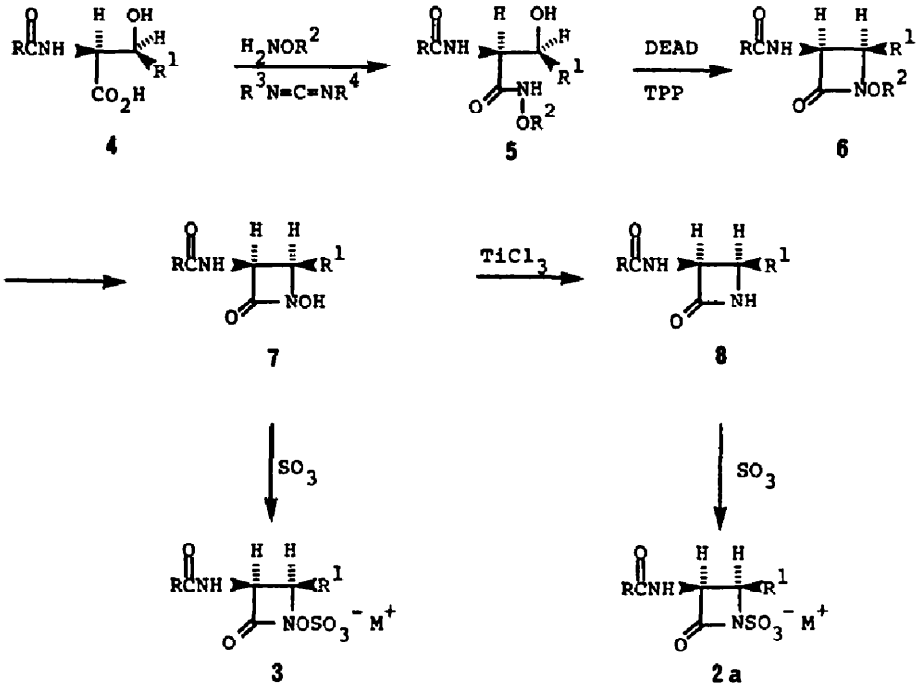
We previously described an efficient hydroxamate mediated approach to the synthesis of N-unsubstituted β-lactams (Scheme 1, **4**→**8**).[4] This route and various modifications have subsequently been used for the synthesis of nocardicins,[5] and the monobactams.[2] Early in the development of this methodology, we were also impressed with the chemical uniqueness of some of the hydroxamate intermediates. For example, the facile ionization of **7** (pK = 5–7)[4] was anticipated to mimic the ionizable carboxyl group of the traditional β-lactam antibiotics.

Although preliminary biological tests of various substituted N-hydroxy-2-azetidinones were discouraging,[6] the subsequent disclosure of the structure of the monobactams did indicate that other ionizable groups could indeed substitute for the unusual carboxylate. Since, in the monobactams, the negative charge is positioned one atom closer to the N-atom than in the classical antibiotics, analogs with a one atom spacer were logical synthetic targets. Any of a variety of spacers may be appropriate, but our initial choice was to retain the activation of the β-lactam ring induced by direct attachment of a heteroatom. Thus, reaction of the N-hydroxy β-lactam **7** with pyridine·SO_3 provided the surprisingly stable N-hydroxy-O-sulfonated-2-azetidinone **3**.[7] As expected, **3** has significant antibacterial properties.[6,7]

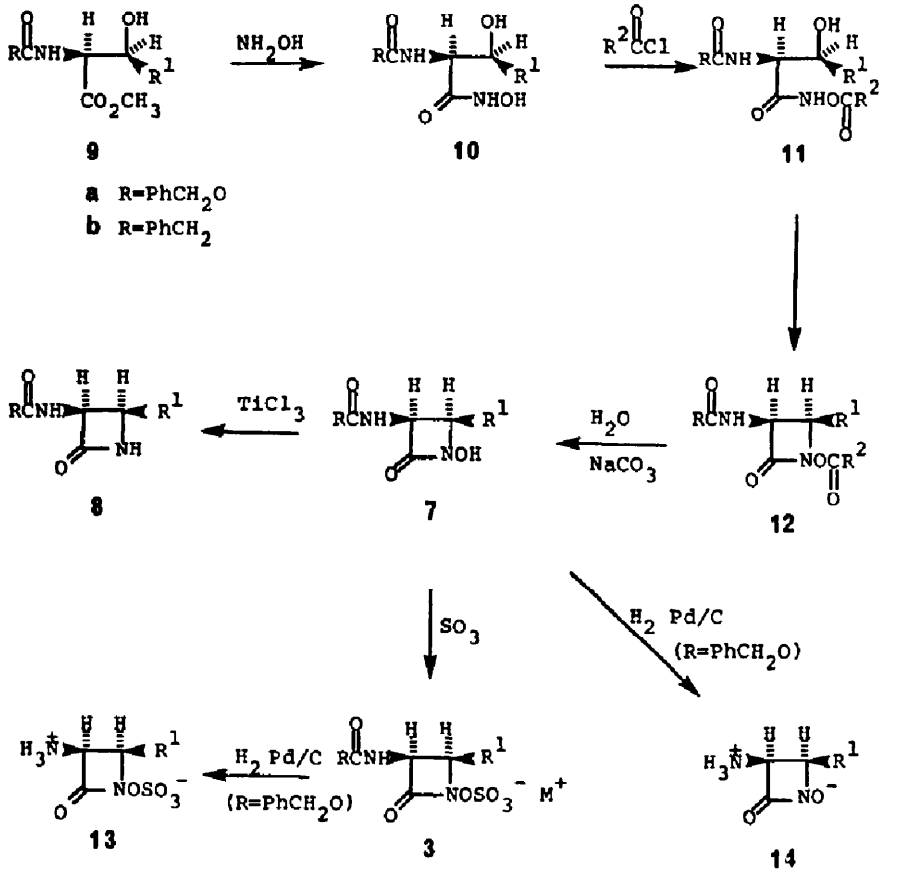
Although high yielding, the route to **3** shown in Scheme 1 is not practical on a large scale. Several chromatographies are employed. The O-substituted hydroxylamines (H_2NOR^2) are expensive or must be prepared separately. The conversion of **4** to **5** is most efficient when done at a controlled pH in aqueous solutions with expensive water soluble carbodiimides. Finally, if R of the acyl group on the 3-amino position is a simple alkyl group (i.e. R = $PhCH_2$) formation of oxazolines is sometimes competitive with cyclization of **5** to **6**.[4]

We have now developed a simplified hydroxamate approach to β-lactam synthesis which circumvents most of these shortcomings, and should be commercially viable. This process, summarized in Scheme 2, differs from that of Scheme 1 primarily in the method of preparing the acyclic hydroxamates **11**.

Thus, reaction of an N-protected β-hydroxy-α-amino acid ester **9** with free hydroxylamine provides the O-unsubstituted hydroxamate **10** directly. In our hands, the direct reaction of O-substituted hydroxylamines (H_2NOR) with normal esters is inefficient. In any event, the O-substituted hydroxylamines are expensive or, in some cases, unstable. Acylation of **10** with a variety of acyl groups provides the crystalline O-protected hydroxamates **11** in good yield. In contrast to the previously used O-pivaloylhydroxylamine,[4] the choice of the acyl group (i.e. R^2 of **12** = Me or Ph) was made to facilitate



Scheme 1.

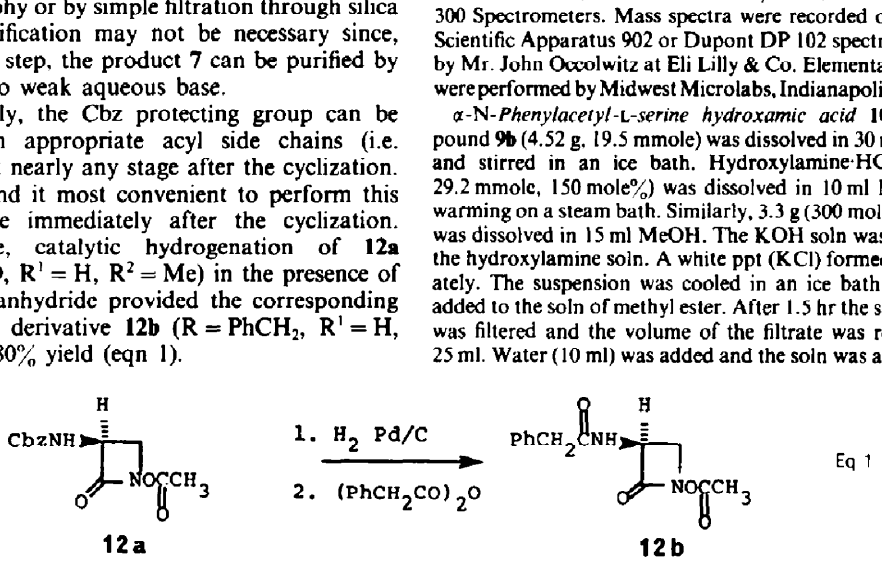


Scheme 2.

eventual solvolytic removal (**12**→**7**). These first two steps (**9**→**10**→**11**) can also be combined and performed in one pot, but the yields are often more variable (30–65%). In either case, no chromatographic purification is required.

The cyclization of **11** to the β-lactam **12** was accomplished by the previous methods[4] in good yields. Although O-acylhydroxamates are susceptible to the Lossen rearrangement,[8] this side reaction is not competitive with the DEAD/TPP or TPP/Et_3N/CCl_4 mediated cyclization. As before, when the 3-amino group is protected with a carbamate (i.e. **11a**→**12a**) the TPP/Et_3N/CCl_4 combination is the preferred set of reagents, but if R is a simple acyl group (i.e. **11b**→**12b**), the use of azodicarboxylates and TPP was more efficient. However, competitive oxazoline formation was still a severe problem. For economical reasons, diisopropylazodicarboxylate (DIAD) was used instead of the diethyl analog (DEAD). The β-lactams were usually purified by medium pressure chromatography or by simple filtration through silica gel. This purification may not be necessary since, after the next step, the product **7** can be purified by extraction into weak aqueous base.

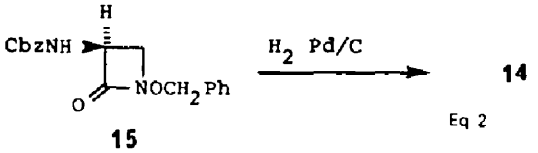
Conceptually, the Cbz protecting group can be replaced with appropriate acyl side chains (i.e. $PhCH_2CO$) at nearly any stage after the cyclization. We have found it most convenient to perform this acyl exchange immediately after the cyclization. For example, catalytic hydrogenation of **12a** (R = $PhCH_2O$, R^1 = H, R^2 = Me) in the presence of phenylacetic anhydride provided the corresponding phenyl acetyl derivative **12b** (R = $PhCH_2$, R^1 = H, R^2 = Me) in 80% yield (eqn 1).



12a **12b** Eq 1

Solvolysis of **12** provided the key N-hydroxy-2-azetidinones **7** cleanly. In contrast to the O-pivaloyloxy-2-azetidinones, any of a variety of mild solvolytic conditions can be employed. Convenient systems include aqueous carbonate or ammonium acetate. As before, $TiCl_3$ mediated N–O reduction provided the N-unsubstituted-2-azetidinones.[9] Noteworthy, is the overall ease of obtainment of the 3-(N-Cbz)-amino-2-azetidinone (**8a**, R^2 = H). Previously, this useful intermediate for the synthesis of the monobactams and 3-amino-nocardicinic acid (3-ANA) was not as readily available.[2,9]

Catalytic hydrogenation of **7a** provided the parent 3-amino-N-hydroxy-2-azetidinone **14**. Compound **14** was also obtained in low yield (30%) by hydrogenation of 3-(N-Cbz)-amino-N-benzyloxy-2-axetidinone **15** (eqn 2). Titration of **14** revealed that it exists in zwitterion form with pKs ≈ 5.2 and 7.2.



15 Eq 2

As described earlier, treatment of **7** with pyridine-SO_3 provided the desired O-sulfonated N-hydroxy-2-azetidinones **3** which were best isolated and purified by the ion pair extraction procedure employed during the preparation of monobactams by the Squibb group.[2] Hydrogenation of **3a** (R^1 = H), also should provide **13**, the parent compound of this novel class of antibiotics.

In conclusion, Scheme 2 represents a practical approach to useful β-lactams and intermediates. No expensive reagents are used and a minimal amount of chromatography is employed.

EXPERIMENTAL

General comments. M.ps were taken on a Thomas–Hoover mp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 727b spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ with TMS as a reference, unless otherwise stated, on Varian EM 390, XL-100 or Nicolet NB 300 Spectrometers. Mass spectra were recorded on an AEI Scientific Apparatus 902 or Dupont DP 102 spectrometer or by Mr. John Occolwitz at Eli Lilly & Co. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN.

α-N-Phenylacetyl-L-serine hydroxamic acid **10b**. Compound **9b** (4.52 g, 19.5 mmole) was dissolved in 30 ml MeOH and stirred in an ice bath. Hydroxylamine·HCl (2.03 g, 29.2 mmole, 150 mole%) was dissolved in 10 ml MeOH by warming on a steam bath. Similarly, 3.3 g (300 mole%) KOH was dissolved in 15 ml MeOH. The KOH soln was added to the hydroxylamine soln. A white ppt (KCl) formed immediately. The suspension was cooled in an ice bath and then added to the soln of methyl ester. After 1.5 hr the suspension was filtered and the volume of the filtrate was reduced to 25 ml. Water (10 ml) was added and the soln was acidified to an apparent pH of 3 with 6N HCl. The mixture was cooled in an ice bath and the resulting crystals were removed by filtration. Recrystallization from EtOH–ether gave 3.06 g (67%) of analytically pure **10b**. M.p. 169.5–171° d; IR (KBr) 3205 cm^{-1}, 1630 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$ + CD_3OD) δ 3.61 (s, 2H), 3.74 (d, 2H), 4.38 (m, 1H), 7.32 (s, 5H). (Found: C, 55.37; H, 6.10; N, 11.78. Calc for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.78%).

O-Acetyl-α-N-Cbz-L-serine hydroxamate **11a**. Compound **9a** (1.27 g, ~5 mmole) was dissolved in 10 ml MeOH and stirred magnetically while being cooled in an ice bath. In separate flasks, 400 mg (5.76 mmole) hydroxylamine hydrochloride and 0.7 g KOH were dissolved in 10 ml portions of MeOH by gently warming on a steam bath and then cooling back to room temp. The KOH soln was added to the hydroxylamine soln. A ppt (KCl) formed immediately. The suspension was added to the soln of the serine methyl ester. After 5 min, one drop fo the mixture was removed and added to a 1% $FeCl_3$aq. Immediate formation of a dark red color indicated formation of some of **10a**. Aliquots were removed after 10 and 20 min. TLC analysis (EtAc/silica gel) indicated that a small amount of starting material remained. After a total of 45 min, 1.0 ml of Ac_2O was added. After another 10 min, an aliquot tested with $FeCl_3$aq revealed the presence of free acid **10a**, so another 0.1 ml of Ac_2O was added. Immediate subsequent $FeCl_3$ analysis was negative. (If the analysis soln is allowed to stand a routine $FeCl_3$ test results, apparently from hydrolysis of **11a**→**11b**. Thus, the test should be

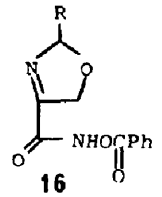
viewed immediately and the reaction not allowed to continue or variable yields will be obtained). The mixture was poured into a separatory funnel containing 20 ml of 5% Na_2CO_3 and 50 ml of EtOAc. The aqueous layer was withdrawn and the organic layer was extracted with two more 15 ml portions of 5% Na_2CO_3. The combined aqueous layers were placed in a separatory funnel over 25 ml of CH_2Cl_2. The aqueous layer was acidified to pH ~ 4–5 by the dropwise addition, with swirling of 6N HCl. The layers were separated and the aqueous was extracted with three more 25 ml portions of CH_2Cl_2. The CH_2Cl_2 layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give 915 mg of a white solid (63%). Recrystallization from EtOAc–hexanes gave an analytical sample, m.p. 120–121° (appeared to sinter at 110°–119°). IR (KBr) 1700 cm^{-1} (broad); ^1H NMR ($CDCl_3$, 90 MHz) 2.15 (s, 3H), 3.5–4.1 (m, 3H, OH + CH_2), 4.35 (m, 1H), 5.1 (s, 2H), 6.1 (br d, NH), 7.33 (s, 5H). (Found: C, 52.56; H, 5.71; N, 9.51. Calc for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.45%).

O-Benzoyl-α-N-phenylacetylserine hydroxamate **11b** (R^2 = Ph). Hydroxamic acid **10b** (0.497 g, 2.09 mmol) was dissolved in 35 ml of MeOH along with 0.32 ml (2.3 mmole, 110 mole%) of Et_3N and stirred at room temp. Benzoyl chloride (0.242 ml, 2.085 mmol, 100 mole%) was added dropwise. After 10 min, a $FeCl_3$ test was negative, and therefore indicated that all of the starting material had been consumed. The mixture was poured into a separatory funnel containing 125 ml of EtOAc and 20 ml of H_2O. The organic layer was washed once more with 10 ml of H_2O, then dried over $MgSO_4$, filtered and evaporated. The white solid residue was recrystallized from EtOAc-hexanes to provide 0.628 g (88%) of **11b**, m.p. 137–139°; IR (KBr) 1760, 1640 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD) δ 3.66 (s, 2H), 3.89 (d, 2H), 4.65 (1H, partially obscured by OH peak), 7.34 (s, 5H), 7.63 (m, 3H), 8.14 (m, 2H).

N-acetoxy-3-(Cbz-amino)-2-azetidinone **12a** (R^1 = H, R^2 = Me). Hydroxamate **11a** (1.184 g, 4 mmole) was dissolved in 30 ml of dry acetonitrile containing 1 ml of CCl_4. Triphenylphosphine (TPP, 4.2 mmole) and Et_3N (4.4 mmole) were added simultaneously. The mixture was stirred at room temp under a drying tube. The reaction was followed by TLC (EtOAc on silica gel, product R_f ~ 0.6). After 8 hr the TPP (R_f ~ 0.7) was nearly depleted so the mixture was concentrated to 2–3 ml and applied to a small Michael–Miller column of silica gel (40–63 μ). Elution with EtOAc-hexanes at 30 ml/min gave several UV active fractions containing the desired product. Evaporation of the solvent gave 734 mg (66%) of **12a** as a white solid (yields have varied, but 60–70% yields are routinely obtained). Recrystallization from EtOAc–hexanes gave the analytical sample, m.p. 130–131°. ^1H NMR (90 MHz) δ 2.13 (s, 3H), 3.53 (dd, 1H), 3.95 (dd, apparent t, 1H), 4.8 (m, 1H), 5.1 (s, 2H), 5.7 (d, NH), 7.33 (s, 5H). IR (KBr) 3350 (br), 1820, 1710 cm^{-1}. (Found: C, 55.86; H, 5.21; N, 10.04. Calc for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.06%).

Attempted cyclization of **11b** *to* **12b** (R^1 = H, R^2 = Ph). Compound **11b** (R = $PhCH_2$, R^1 = H, R^2 = Ph; 0.31 g, 0.89 mmole) was dissolved in 25 ml of THF along with 0.26 g (0.99 mmole, 110 mole%) of Ph_3P and 0.193 ml of DIAD (0.978 mmole, 110 mole%). After stirring for 1 hr at room temp under N_2, the solvent was evaporated to leave a yellow oil. Chromatography on silica gel with EtOAc–hexanes (1:1) gave **12b** and the corresponding oxazoline **16** in 65% yield in a 1:5 ratio. The desired product was recrystallized from EtOAc–hexanes to provide **12b** in 6% yield, m.p. 127.5–130°; IR (KBr) 1795, 1760, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 2H), 3.72 (m, 1H), 4.15 (m, 1H), 5.15 (m, 1H), 6.10 (m, 1H), 7.26–8.04 (m, 10H).

Conversion of **12a** *to* **12b** (R^1 = H, R^2 = Me). Compound **12a** (R = $PhCH_2O$, R^1 = H, R^2 = Me; 28 mg, 0.1 mmole) was dissolved in 8 ml of EtOAc under N_2. Pd–C (25 mg of 5%) and 25.5 mg (0.1 mmol of phenylacetic anhydride were added and H_2 was slowly passed over the stirred mixture. After 2 hr, the catalyst was removed by filtration and washed with



16

20 ml of EtOAc. The combined EtOAc was extracted with 25 ml of 5% $NaHCO_3$ to remove the phenylacetic acid. The organic layer was washed with brine (20 ml), dried over $MgSO_4$, filtered and evaporated to provide 25 mg of a white solid. Recrystallization from EtOAc–hexanes gave 22.4 mg of **12b**, m.p. 147–149°; R_f [silica with EtOAc–hexanes (8:2)] = 0.5; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.56 (br s, 3H), 3.96 (apparent t, 1H), 4.92 (m, 1H), 6.92 (br d, NH), 7.33 (s, 5H); IR (KBr) 3440 (br), 1810, 1770, 1650 cm^{-1}. Mass spec (FD) *m/e* 263 (M + 1).

3-(Cbz-Amino)-N-hydroxy-2-azetidinone **7a**[10]

Method A. The acetyl derivative **12a** (139 mg, 0.5 mmole) was suspended in 8 ml of MeOH–water (2:1) at 0°. The mixture was stirred vigorously and 135 mg (1.25 mmole) of solid Na_2CO_3 was added. After 15 min, an aliquot was removed for TLC analysis (EtOAc on silica gel) and showed two spots (R_f = 0.6 corresponding to starting **12a** and R_f = 0.2–0.3 for product). After 30–45 min, the starting **12a** was no longer visible upon TLC analysis. The apparent pH of the mixture was adjusted to pH 5 with 1.0N HCl. Extraction with four 25 ml portions of EtOAc, followed by drying the combined extracts with brine and $MgSO_4$, and evaporation gave 101 mg (85.6%) of **7a** as a white solid, m.p. 149–150° d. IR (KBr) 3250 br, 1780, 1740, 1700 cm^{-1}. ^1H NMR (90 MHz in acetone-D_6) δ 3.3 (dd, 1H), 3.64 (apparent t, 1H), 4.50 (m, 1H), 4.97 (s, 2H), 6.97 (m, 1H), 7.33 (s, 5H). ^1H NMR (90 MHz in DMSO-D_6) 3.35 (dd, 1H), 3.7 (apparent t, 1H), 4.5 (m, 1H), 5.1 (s, 2H), 7.4 (s, 5H), 8.05 (br d, NH), 10.3 (br, OH). (Found: C, 55.89; H, 5.34; N, 11.67. Calc for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.85%).

Method B. Compound **15**[4] (1.0 g, 3.07 mmole) was dissolved in 15 ml THF and 7.5 ml water was added. The homogeneous soln was purged with N_2 for 5 min then 60 mg of 5% Pd–C was added. The suspension was stirred while H_2 was bubbled through slowly. The reaction was followed by TLC analysis (EtOAc on silica gel; **15** had an R_f of 0.6). After 1 hr, TLC revealed one component at R_f = 0.6 and one at R_f = 0.3 (corresponding to **7a**). After 3.5 hr the TLC revealed no R_f 0.6 spot, but the R_f 0.3 spot remained. N_2 was passed through the system for 10 min and then the suspension was filtered off. The filtrate was concentrated to remove the THF. The aqueous layer was extracted with three 15 ml portions of CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$ filtered and evaporated to give 140 mg (19%) of a white solid which was identical to that prepared by method A.

Hydrogenation of **15** in MeOH or for longer times in THF–H_2O also provides **14**. However, as described later, **14** is more efficiently obtained by hydrogenation of **7a**.

3-Phenylacetamido-N-hydroxy-2-azetidinone **7b**.[10] Compound **6**[4] (R = $PhCH_2$, R^1 = H, R^2 = CH_2Ph; 234 mg, 0.75 mmole) was dissolved in 25 ml of MeOH along with 49.8 mg of 5% Pd–C. H_2 gas was bubbled through the soln for 1 hr. The catalyst was removed by filtration and the solvent was evaporated. The residue was recrystallized from EtOAc–hexanes to provide 121.4 mg (74%) of **7b**, m.p. 138–140° d; pK = 6.5; IR (KBr) 3230, 3050, 2800 (all broad), 1770, 1720, 1655 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.28 (dd, 1H), 3.46 (s, 2H), 3.7 (apparent t, 1H, J = 5 Hz), 4.7 (m, 1H), 7.32 (s, 5H), 8.85 (d, br NH), 10.22 (s, br OH).

3-(Cbz-Amino)-2-azetidinone **8a**. Compound **7a** (118 mg, 0.5 mmole) was dissolved in a soln of 10 ml THF and 10 ml of water at pH 7 under N_2 in a magnetically stirred flask fit-

ted with a pH electrode. A soln of 0.8 ml (1 mmole) of 20% aqueous $TiCl_3$ (MCB) was added dropwise from a syringe. As required during the addition, 3.0N NaOH was added from an attached buret to maintain the pH at 7.0. After the addition was complete, stirring was continued for 2 hr. The aqueous mixture was adjusted to pH 8, transferred to a separatory funnel and extracted with three 25 ml portions of EtOAc. The combined EtOAc was washed with 10 ml of brine, dried over $MgSO_4$, filtered and evaporated. The residue was recrystallized from EtOAc–hexanes to give 69 mg (60%) of white solid, m.p. 160–161° (lit[2] m.p. 161°). ^1H NMR (acetone d_6) δ 2.86 (m, 1H), 3.23 (dd, 1H), 3.46 (apparent t, 1H), 4.8 (m, 1H), 5.07 (s, 2H), 7.0 (m, 1H), 7.36 (s, 5H). IR (KBr) 1740, 1700 cm^{-1}.

3-*Amino*-N-*hydroxy*-2-*azetidinone* **14**. The Cbz-precursor **7a** (236 mg, 1 mmole) was dissolved in 15 ml of THF-H_2O (1:1) and flushed with N_2. Pd/C (15 mg of 5%) was added and H_2 was bubbled through the suspension. After 1 hr at room temp, no UV active spots were visible upon TLC analysis. The catalyst was removed by filtration. The THF was evaporated and the remaining aqueous soln was lyophilized to give 99 mg (99%) of **14** as a white solid. M.p. 250° (decomposed to a dark brown solid). The compound gives a positive $FeCl_3$ test in MeOH and a positive ninhydrin test. Titration indicated pK values of 5.2 and 7.2. IR (KBr) 3550 (broad) 1740, 1640 cm^{-1}; ^1H NMR (D_2O) 3.5 (dd, 1H), 3.87 (apparent t, 1H), 4.27 (m, 1H).

2-*Oxo*-3(*Cbz-amino*)-1-*azetidinyl sulfate, tetra n-butyl ammonium salt* **3a** [$M^- = (nBu)_4\overset{+}{N}$]. Compound **7a** (100 mg, 0.423 mmole) was added to 2 ml dry pyridine containing 200 mg (0.125 mmole) pyridine·SO_3. The suspension was stirred for 6 hr at room temp. The pyridine was evaporated and the residue was dissolved in 50 ml of 0.5 M KH_2PO_4. This aqueous soln was washed with three 20 ml portions of EtOAc to remove any organic soluble impurities. To the aqueous phase was added 108 mg (0.317 mmole) of tetrabutylammonium hydrogen sulfate. Extraction with four 60 ml portions of CH_2Cl_2 followed by drying over $MgSO_4$, filtration and evaporation gave 150 mg (70%) of **3a** as a thick oil. ^1H NMR ($CDCl_3$) δ (m, 12H), 1.53 (m, 16H), 3.23 (m, 8H), 3.74 (dd, 1H), 4.1 (apparent t, 1H), 4.76 (m, 1H), 5.1 (s, 2H), 6.17 (br d, 1H), 7.4 (s, 5H). The compound turns brown upon prolonged storage at room temp.

Acknowledgements—We are grateful for support from the National Institutes of Health (NIH) and Eli Lilly & Co. The 300 MHz NMR system used was obtained from grants received from the NIH and the University of Notre Dame.

REFERENCES

[1]Fellow of the Alfred P. Sloan Foundation 1981–83.
[2]D. M. Floyd, A. W. Fritz and C. M. Cimarusti, *J. Org. Chem.* **47**, 176 (1982); C. M. Cimarusti, H. E. Applegate, H. W. Chang, D. M. Floyd, W. H. Koster, W. A. Slusarchyk and M. G. Young, *Ibid.* **47**, 179 (1982).
[3]A. Smada, K. Kitano, K. Kinataka, M. Murai and M. Asai, *Nature* **289**, 590 (1981).
[4]M. J. Miller, P. G. Mattingly, M. A. Morrison and J. F. Kerwin, *J. Am. Chem. Soc.* **102**, 7026 (1980).
[5]P. G. Mattingly and M. J. Miller, *J. Org. Chem.* **46**, 1557 (1981).
[6]Unpublished biological testing results performed at Eli Lilly & Co., Indianapolis, IN.
[7]Subsequent to our preparation of **3** a related patent appeared from the Squibb Group (U.S. Patent 4,337,197).
[8]M. J. Miller, F. E. DeBons and G. M. Loudon, *J. Org. Chem.* **42**, 1750 (1977).
[9]P. G. Mattingly and M. J. Miller, *Ibid.* **45**, 410 (1980).
[10]Care should be exercised to insure that the N-hydroxy-β-lactams are not heated during the reaction or workup (including solvent evaporation) since these compounds are susceptible to thermal rearrangement: T. Hirose, K. Chiba, S. Michio, J. Nakano and H. Uno, *Heterocycles* **19**, 1019 (1982).