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HETEROATOM ACTIVATED β-LACTAM ANTIBIOTICS: SYNTHESIS OF BIOLOGICALLY ACTIVE SUBSTITUTED N-OXY-3-AMINO-2-AZETIDINONES (OXAMAZINS)

by

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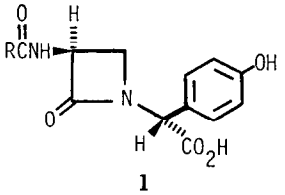
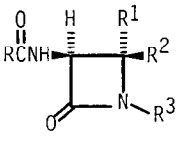
Representatives of a new class of oxygen activated β-lactams (oxamazins) have been synthesized from N-hydroxy-3-amino-2-azetidinones. The oxamazins show significant activity predominantly against Gram negative bacteria.

The discovery of the nocardicins 1[1] and monobactams 2[2] (sulfazecin)[3] has generated considerable interest in the synthesis of novel monocyclic β-lactams. Quite early in our development of an efficient hydroxamate mediated synthesis of substituted N-hydroxy-2-azetidinones 3[4] we recognized the unique properties of this class of compounds. While the N-hydroxy compounds themselves are unusually acidic and prone to rearrangement,[5] the O-substituted derivatives are usually more susceptible to nucleophilic attack at the β-lactam carbonyl than are the corresponding N-alkyl β-lactams. The intriguing question was whether this heteroatom induced chemical activation could be used to provide new biologically active compounds. The first indication of the feasibility of this concept was the significant biological activity of the monobactams, which contain a N-S linkage. Subsequently, the Squibb group,[6] our own laboratory,[7] and several others have independently described the synthesis of the biologically active O-sulfated-N-hydroxy-2-azetidinones (monosulfactams, 4). Herein we report the synthesis of the oxamazins, 5, a totally synthetic class of heteroatom activated β-lactam antibiotics.[8]



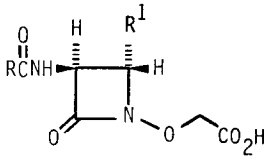
1



2 $R^3=SO_3^-$

3 $R^3=OH$

4 $R^3=OSO_3^-$



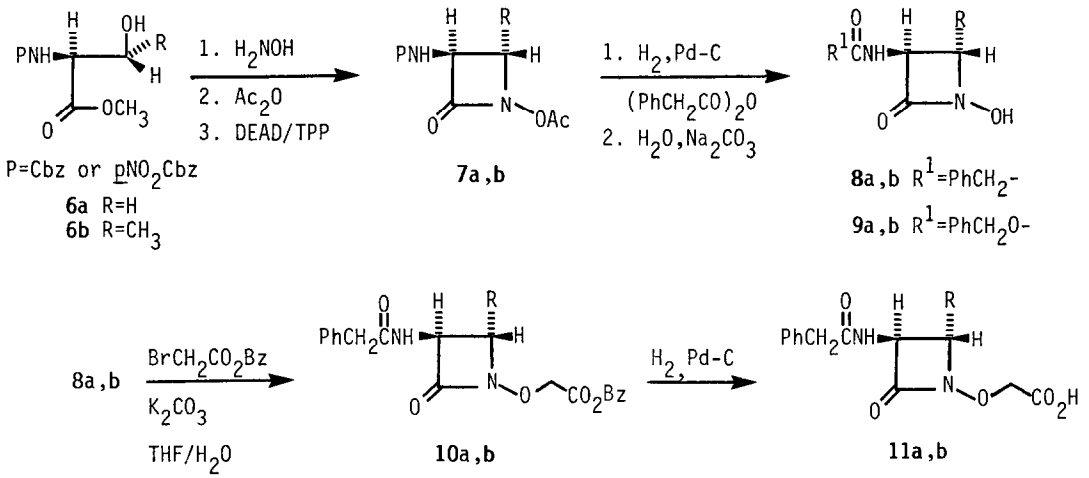
5

oxamazins

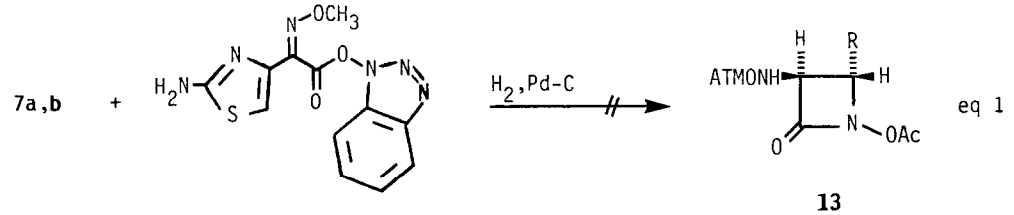
The key step in the preparation of the oxamazins is the alkylation of N-hydroxy-2-azetidinones with haloacetate esters. We have found this method to be simpler and more versatile than the separate synthesis of individual α-aminooxyacetate esters, coupling with N-protected amino acids and cyclization.[4,9] Thus, N-hydroxy-2-azetidinones **8a,b**, prepared from serine and threonine,[7] were treated with benzyl bromoacetate and K_2CO_3 in THF/H_2O (1:1) to provide the benzyl esters **10a** (35%) and **10b** (52%) respectively.[10,11] Catalytic hydrogenation of **10a,b** provided the corresponding phenylacetamido oxamazins **11a** and **11b** in 71-75% yields.

Preliminary antibacterial tests on salts of **11** prompted us to replace the phenylacetyl group with the more biologically responsive aminothiazole methyl oxime (ATMO) side chain.

Scheme 1



Introduction of the ATMO side chain by transacylation (i.e. **7** + **12** → **13**) was attempted first, but failed since the Cbz group of **7a** could not be removed by hydrogenation in the presence of the sulfur containing ATMO active ester. Replacement of the Cbz group with p-nitrobenzyl carbamate still did not facilitate the hydrogenation (eq. 1). We therefore turned our attention to introduction of the side chain after the oxamazin nucleus had been prepared.

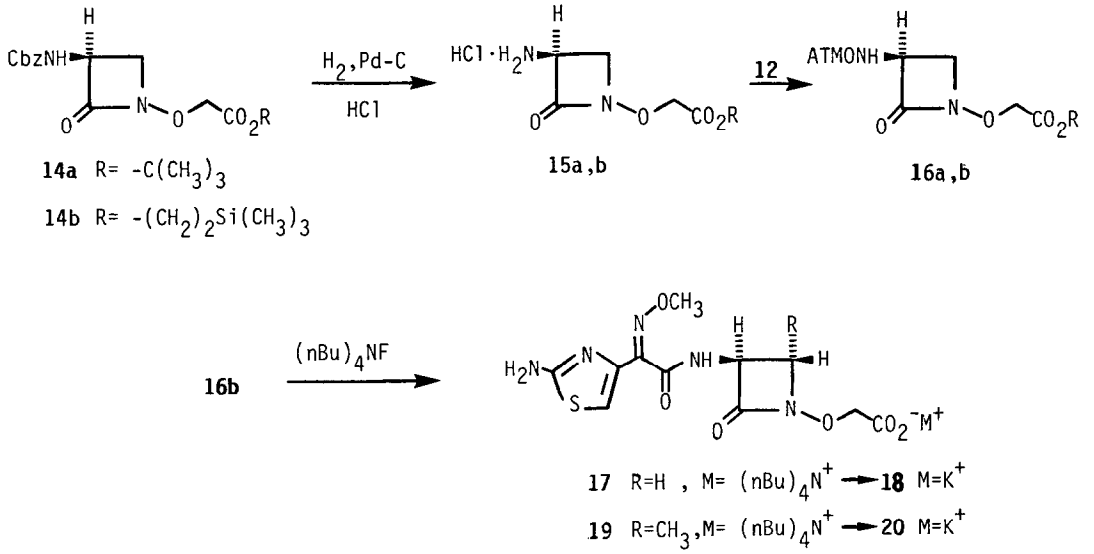


12 ATMO-OHBT

13

Alkylation of the protected N-hydroxy-2-azetidinones **9a,b**[7] with either t-butyl- or trimethylsilylethyl bromoacetates proceeded as expected to give **14a** and **14b** respectively. In each case, the Cbz group was removed with H_2, Pd-C in ethanol containing one equivalent of HCl to give the salts **15a** and **15b** (Scheme 2). Separate reaction of **15a** and **15b** with the ATMO active ester **12** gave the acylated products **16a** and **16b** in good yields. All attempts to cleave the t-butyl ester of **16a** gave predominant opening of the β-lactam ring. However, treatment of **16b** with $(nBu)_4N^+F^-$ cleanly removed the trimethylsilylethyl ester to give the $(nBu)_4N^+$ salt **17**. Ion exchange chromatography (Dowex, K^+) provided the potassium salt **18**. The 4-methyl derivatives **19** and **20** were prepared in the same manner from L-threonine.

Scheme 2



The oxamazins **18** and **20** are structurally noteworthy since the ionizable carboxyl group is displaced one atom further from the β-lactam nitrogen than in the penicillins, cephalosporins, and nocardicins (two atoms further from the nitrogen than in the monobactams). Yet, apparently because of the activating affect of the N-O bond, these simple compounds show good to potent activity against Gram negative bacteria. Syntheses of appropriate analogues are in progress.

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References and Notes

‡ Fellow of the Alfred P. Sloan Foundation, 1981-1985. Recipient of a NIH Career Development Award (1983-1988).

1. Hashimoto, M.; Konori, T.; Kamiya, T. A. J. Am. Chem. Soc. **1976**, 98, 3023. Kamiya, T. "Recent Advances in the Chemistry of β-Lactam Antibiotics"; Chemical Society: Cambridge, England, **1976**, pp. 287-294.
2. Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S. Nature **1981**, 291, 489. Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. J. Org. Chem. **1982**, 47, 176. Cimarusti, C. M.; Applegate, H. E.; Chang, H. W.; Floyd, D. M.; Koster, W. H.; Slusarchyk, W. A.; Young, M. G. J. Org. Chem. **1982**, 47, 179.
3. Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. Nature **1981**, 289, 590.

4. Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F.; J. Am. Chem. Soc. **1980**, 102, 7026.
5. Hirose, T.; Chiba, K.; Mishio, S.; Nakano, J.; Ono, H. Heterocycles **1982**, 19, 1019.
6. Gordon, E. M.; Ondetti, M. A.; Pluscec, Jelka; Cimarusti, C. M.; Bonner, D. P.; Sykes, R. B. J. Am. Chem. Soc. **1982**, 104, 6053.
7. Miller, M. J.; Biswas, A.; Krook, M. A. Tetrahedron **1983**, 39, 2571.
8. The term oxamazin is derived from N-oxy-3-amino-2-azetidinone.
9. Atherton, F. R.; Lambert, R. W. Tetrahedron **1984**, 40, 1039. This paper reported a derivative of 5 and prompted the disclosure of our results.
10. The alkylations were not as efficient with the same base in CH_3CN.
11. A partial list of characterization data includes: **10a**, colorless oil; 35% yield; ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.4 (s, 5H), 7.3 (s, 5H), 6.5 (bd, 1H), 5.2 (s, 2H), 4.6 (m, 1H), 4.5 (s, 2H), 3.9 (t, 1H), 3.5 (bs, 3H total); IR (in $CDCl_3$) 1760, 1650 cm^{-1}. **10b**, colorless oil; 52% ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.4 (s, 5H), 7.3 (s, 5H), 6.95 (bd, 1H), 5.2 (s, 2H), 4.55 (s, 2H), 4.2 (dd, 1H), 3.85 (m, 1H), 3.55 (s, 2H), 1.45 (d, 3H); IR (in $CDCl_3$) 1760, 1650 cm^{-1}. **11a**, white solid, M.P. 108-110°C; 71%; ^{1}HNMR (d_6 acetone, 90 MHz) δ = 8.1 (bd, 1H), 7.45 (s, 5H), 6.6-7.0 (bs, 1H), 4.8 (m, 1H), 4.55 (s, 2H), 3.9 (t, 1H), 3.6 (m, 1H), 3.5 (s, 2H); IR (KBr) 3700-2900, 1770 cm^{-1}. **11b**, colorless oil; 75%; ^{1}HNMR (d_6 acetone, 90 MHz) δ = 7.9-8.3 (b, 3H), 7.5 (s, 5H), 4.6 (s, 2H), 4.35 (m, 1H), 4.0 (m, 1H), 3.6 (s, 2H), 1.4 (d, 3H); IR (neat) 3700-2800, 1770 cm^{-1}. **14a**, while solid, M.P. 80-83°C; 55%; ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.35 (s, 5H), 6.4 (bd, 1H), 5.1 (s, 2H), 4.55 (b, 1H), 4.3 (s, 2H), 3.85 (t, 1H), 3.6 (dd, 1H), 1.4 (s, 9H); IR (in $CDCl_3$) 1780, 1730 cm^{-1}. **14b**, colorless oil; 84%; ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 7.65 (s, 5H), 6.55 (d, 1H), 5.2 (s, 2H), 4.7 (m, 1H), 4.6 (s, 2H), 4.35 (t, 2H), 3.95 (t, 1H), 3.7 (m, 1H), 1.0 (t, 2H), 0.0 (s, 9H); IR (neat) 1785, 1720 cm^{-1}. **15a**, while solid, M.P. d > 150°C; 100%; ^{1}HNMR (d_4 MeOH, 90 MHz) δ = 4.80 (s, 3H), 4.33 (s, 2H), 4.25 (m, 1H), 3.95 (t, 1H), 3.66 (dd, 1H), 1.25 (s, 9H); IR (KBr) 3200-2500, 1770, 1740 cm^{-1}. **16a**, yellow solid, M.P. d < 100°C; 77%; ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.7 (d, 1H), 6.65 (s, 1H), 6.0 (bs, 2H), 5.2 (b, 1H), 4.4 (s, 2H), 4.2-3.4 (m, 5H total), 1.4 (s, 9H); IR (in $CDCl_3$) 1780, 1740 cm^{-1}. **16b**, yellow oil; 76%; ^{1}HNMR ($CDCl_3$, 90 MHz) δ = 8.9 (d, 1H), 6.9 (s, 1H), 6.0 (bs, 2H), 5.3 (m, 1H), 4.7 (s, 2H), 4.35 (t, 2H), 4.25 (t, 1H), 4.1 (s, 3H), 3.9 (dd, 1H), 1.0 (t, 2H), 0.0 (s, 9H); IR (in $CDCl_3$) 1780, 1750 cm^{-1}. **18**, yellow solid; 93%; ^{1}HNMR (D_2O, 90 MHz) δ = 7.1 (s, 1H), 5.0 (m, 1H), 4.5 (s, 2H), 4.2 (t, 1H), 4.0 (s, 3H), 3.9 (dd, 1H); IR (KBr) 3700-2800, 1760 cm^{-1}. **20**, yellow solid; 72%; ^{1}HNMR (D_2O, 90 MHz) δ = 7.1 (s, 1H), 4.6 (m, 1H), 4.55 (s, 2H), 4.35 (m, 1H), 4.0 (s, 3H), 1.50 (d, 3H); IR (KBr) 3700-2800, 1770 cm^{-1}.

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