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γ-LACTAM ANALOGUES OF CARBAPENEMS

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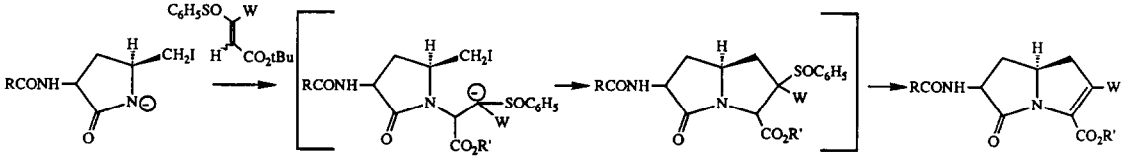
Summary: γ-Lactam analogues of carbapenems have been synthesized using a [3+2] cyclization approach. Slight antibiotic activity was observed in one case.

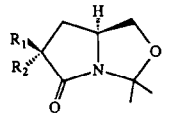
β-Lactam antibiotics' mechanism of action involves active site acylation of key enzymes (penicillin binding proteins≡PBP's) required for bacterial cell wall synthesis.[1] We hypothesized that a suitably activated lactam of a different structural type could be operative in this mechanism and chose the following γ-lactam analogues of carbapenems as synthetic targets.[2]

Central to this hypothesis was the reasoning that electron withdrawing groups (W = CO_2Me,CN) at C-2 would heighten the reactivity of the lactam linkage by delocalization of the lone pair of electrons on the bridgehead nitrogen away from the C-8 carbonyl group.[3,4] Additionally, incorporation of classical cephalosporin side-chains at C-7 (provided such structures proved to be chemically stable[5]) would offer the best opportunity for biological activity by exertion of their well-known influence on PBP binding and outer membrane penetration.

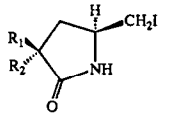
The strategy developed for the synthesis of these compounds is outlined below. Deprotonation of a substituted 5-iodomethylpyrrolidinone and treatment with a β-phenylsulfinyl-β-carboalkoxy (or β-cyano) acrylate should generate stabilized anion i capable of intramolecular alkylation and elimination.[6] The phenylsulfinyl group was chosen upon the prediction that the stabilized anion i would not only facilitate initial Michael reaction but also aid in the alkylation step. Additionally, this disconnection allows for ready preparation of substituted pyrrolidinones from derivatives of S-pyrroglutamic acid, the asymmetry of which has the same absolute configuration as that found in β-lactam antibiotics.



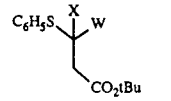
i



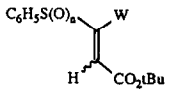
1 $R_1 = R_2 = H$
2 $R_1 = R_2 = NOH$
3a $R_1 = tBOCNH, R_2 = H$
3b $R_1 = H, R_2 = tBOCNH$



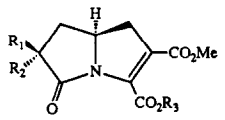
4a $R_1 = tBOCNH, R_2 = H$
4b $R_1 = H, R_2 = tBOCNH$



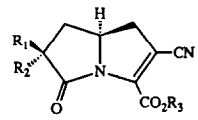
5a X = H, W = CO_2Me
6a X = Cl, W = CO_2Me



7a W = CO_2Me, n = 0
8a W = CO_2Me, n = 1
8b W = CN, n = 1



9a $R_1 = tBOCNH, R_2 = H, R_3 = tBu$
9b $R_1 = H, R_2 = tBOCNH, R_3 = tBu$
11a $R_1 = ATMONH, R_2 = R_3 = H$
11b $R_1 = H, R_2 = ATMONH, R_3 = H$
13 $R_1 = R_2 = H, R_3 = Me$



10a $R_1 = tBOCNH, R_2 = H, R_3 = tBu$
12a $R_1 = ATMONH, R_2 = R_3 = H$

Treatment of S-(+)-5-hydroxymethyl-2-pyrrolidinone[7a] with 2,2-dimethoxypropane and catalytic p-toluenesulfonic acid (toluene, 110°C, 2 hrs) afforded acetonide 1[8] in 65% yield. Reaction of the acetonide with potassium t-butoxide (2.7 equiv) and n-butylnitrite (5.0 equiv, THF, 23°C, 1.5 hrs) provided oxime 2 in 58% yield. Catalytic reduction (10% Pd/C, 70 psi H_2, MeOH, 18 hrs) followed by amine protection (t-BOC_2O, H_2O, $NaHCO_3$) afforded a single carbamate (3a, vide infra) in 54% yield. Although the stereochemistry of the product was predicted to be 3a based on delivery of hydrogen to the convex face of the reactant, a suitable crystal could not be obtained for X-ray analysis. However, reduction of 2 by treatment with zinc (EtOH/HOAc 1:1, 1 hr) followed by formation of the t-BOC derivative as above afforded a 90% yield of a mixture of a different carbamate and the one above in a ratio of ca. 20:1, which was homogeneous after one crystalization. The stereochemistry of this major isomer was shown to be 3b by X-ray crystallography[9] illustrated in Figure 1.

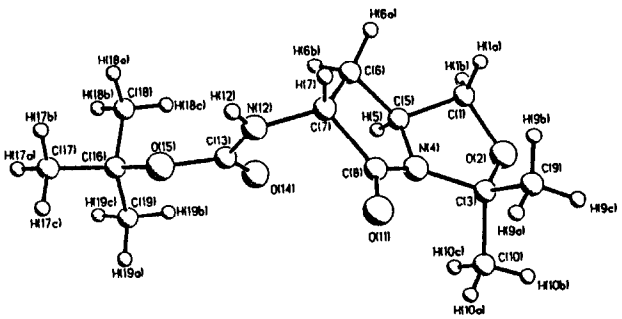


Figure 1.

Both 3a + 3b were converted to the corresponding 5-iodomethyl derivatives 4a and 4b by the three-step sequence: 1) hydrolysis of the acetonide ($HOAc/CH_3CN/H_2O$ 80:15:5, 20 hrs), 2) formation of the mesylate ($MeSO_2Cl$, Et_3N, $CHCl_3$, 2 hrs), and 3) displacement by iodide (NaI, acetone, 60°C, 16 hrs). The overall yields were 44% and 30% respectively.

The sulfoxide annulating reagent 8a was prepared as follows. Alkylation of the lithium anion of methyl phenylthioacetate with t-butyl bromoacetate (THF, -42°C to 23°C, 2 hrs) gave succinate 5a in 80% yield. Treatment of 5a with N-chlorosuccinimide (CCl_4/THF 2:1, reflux, 4 hrs) afforded chloride 6a which was immediately treated with DBU (CH_2Cl_2, -78°C to 23°C, 1.5 hrs) to give 7a as a mixture of isomers in 80% overall yield. Oxidation using peracetic acid (CH_2Cl_2, -42°C to 23°C, 2 hrs) gave sulfoxide 8a in 80% yield. The nitrile reagent 8b was prepared analogously starting with phenylthioacetonitrile in 10% overall yield.[10]

The cyclization reaction was carried out as follows. Treatment of 4a with lithium hexamethyldisilazane (1.1 equiv, THF, -78°C, 20 min) followed by addition of a cold THF solution of sulfoxide 8a (1.2 equiv) with warming to 23°C over 3 hrs afforded γ-lactam 9a in 60% yield.[11] Likewise, nuclei 9b and 10a were prepared in yields of 50% and 70% respectively.

These nuclei were deprotected and acylated by an activated form of the 2-aminothiazol-4-yl-methoximino acetic acid (ATMO) sidechain,[12] a potent activator of cephalosporins. Thus, treatment of 9a with neat trifluoroacetic acid, concentration *in vacuo*, and acylation by treatment with the hydroxybenzotriazole ester of ATMO ($NaHCO_3/H_2O$/acetone) afforded 11a in 34% yield. A similar procedure provided 11b and 12a in 26% and 15% overall yields.

In vitro microbiological testing demonstrated slight activity of 11a vs *E. coli* X161 and X580, while 11b and 12a showed none. The fact that these compounds are active as acylating agents is shown by rapid lactam hydrolysis (versus ester saponification) when 13[13] was treated with one equivalent of lithium hydroxide, a procedure which successfully saponifies esters in some β-lactam systems.[6a] Preparation of other γ-lactam analogues of carbapenems as well as application of this methodology towards the synthesis of other antimicrobials will be the subject of future publications.

Acknowledgment. We would like to thank Dr. M. Hoehne for *in vitro* microbiological studies, Lilly Molecular Structure Research Laboratory for spectroscopic and analytical data, and Drs. L. C. Blaszczak and J. M. Morin, Jr. for helpful discussions.

References and Notes

1. For a general discussion see: Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, N. H.; Waring, M. J. "The Molecular Basis of Antibiotic Action," John Wiley and Sons, Ltd., London, 1981, pp. 79-136.

2. During the course of these studies, other syntheses of γ-lactam analogues of β-lactam antibiotics have appeared a) Baldwin, J. E.; Chan, M. F.; Gallacher, G.; Monk, P.; Prout, K. J.C.S. Chem. Comm. 1983, 250; b) Baldwin, J. E.; Chan, M. F.; Gallacher, G.; Otsuka, M.; Monk, P.; Prout, K. Tetrahedron, 1984, 40, 4513; c) U.S. Patent 4,428,960 (1984); Chem. Abstr., 1984, 100, 191655; d) Baldwin, J. E.; Adlington, R. M.; Jones, R. M.; Schofield, C. J.; Zarocostas, C.; Greengrass, C. W. J.C.S. Chem. Commun., 1985, 194.

3. Boyd, D. B. In "The Chemistry & Biology of β-Lactam Antibiotics. Vol. 1", eds. Morin, R. B. and Gorman, M., Academic Press, New York, 1982, pp 437-545.

4. An adaptation of the conventional numbering of the carbapen-2-em ring system is adopted.

5. For an example of chemical instability in a 6-amino-carbapen-2-em, see Kametaini, T.; Nakayama, A.; Matsumoto, H.; Honda, T. Chem. Pharm. Bull. 1983, 31, 2578.

6. During the course of these studies, similar synthetic methods have appeared: a) Fujimoto, K.; Iwano, Y.; Mirai, K. Tetrahedron Lett., 1984, 25, 1151; b) Mastalerz, H.; Vinet, V. Tetrahedron Lett., 1985, 26, 4315.

7. a) Saijo, S.; Wada, M.; Himiza, J.; Ishida, A. Chem. Pharm. Bull., 1980, 28, 1449; b) Silverman, R. B.; Levy, M. A. J. Org. Chem., 1980, 45, 815.

8. Satisfactory spectral data were obtained for all new compounds.

9. 3b crystallizes from Et_2O as colorless needles in the orthorhombic space group p $2_12_12_1$, with 8 molecules in a unit cell having the dimensions a = 10.720(3) Å; b = 26.477(8) Å; c = 10.569(4) Å; the calculated density was 1.197 g cm^{-3}. The intensities of 2424 unique reflections with 2θ less than 116° were measured on a 4-angle diffractometer using monochromatic copper radiation. The positions of the atoms were obtained by interpretation of an E-map phased by the random tangent routine RANT of the SHELXTL program. The structure was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen atoms which were included at calculated positions. The final R-factor was 0.0701 for 2259 observed reflections. Figure 1 shows one of the two molecules, which have slightly different conformations, in the asymmetric unit.

10. Alkylation of $ØSCH_2CN$ with t-butyl bromoacetate afforded a 20% yield of desired material. The remaining steps in the sequence proceeded in 50% overall yield.

11. The yield in this reaction is not reflective of the olefin isomer ratio. In a related system, pure (E)-sulfoxide 8a gave an identical yield to that using pure (Z)-sulfoxide in side-by-side cyclization reactions. Hornback, W. J.; Munroe, J. E. Unpublished results.

12. Webber, J. A.; Wheeler, W. J. In "The Chemistry and Biology of β-Lactam Antibiotics, Vol. 1", eds. Morin, R. B. and Gorman, M. Academic Press, New York, 1982, pp 371-436.

13. Prepared in 56% yield by treatment of S-5-bromomethylpyrrolidinone[7b] with dimethyl phenylsulfinylfumarate as described in the text.

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