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γ-LACTAM ANALOGUES OF THE PENEMS

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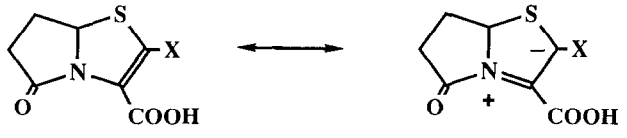
Summary: Racemic γ-lactam analogues of the penems have been prepared and tested for biological activity. The 7-acylamino derivatives exhibited low levels of antibiotic activity.

β-Lactam antibiotics have been shown to exert their biological activity by acylating several specific enzymes involved in the cross-linking of peptidoglycan chains during bacterial cell wall synthesis.[1] The unusual reactivity of the amide bond in β-lactam antibiotics has been attributed to a decrease in amide resonance due to ring strain in the β-lactam such that of the two canonical forms, 1 contributes in a greater proportion than 2 as compared with normal amides.[2]

1 2

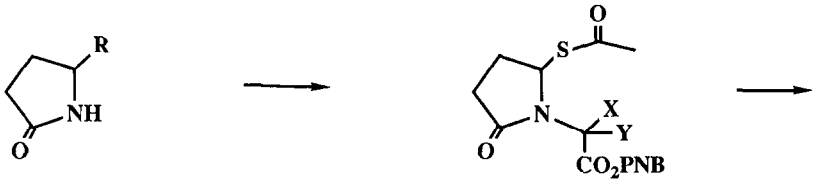
A number of γ- and δ-lactam analogues of β-lactam antibiotics have been prepared, yet none of these derivatives has shown significant antibiotic or β-lactamase inhibitory activity.[3] We decided to design a γ-lactam analogue with a suitably activated amide bond. To this end, we chose to prepare the γ-lactam analogues of the penems where resonance through the double bond in the thiazoline ring might enhance reactivity and hence, biological activity (especially if X is electron withdrawing).[4]



3 4

The 7-unsubstituted γ-lactam derivative 11 was prepared for direct comparison with its known β-lactam analogue 12, which has been shown to be a potent antibiotic substance.[5] Solvolysis of 5-methoxy-2-pyrrolidinone (5)[6] (neat thiolacetic acid, 20 h) afforded a 61% yield of thioacetate 6.[7] The thiazoline ring was elaborated by following the conventional procedure developed by Woodward et al..[5,8] Condensation of 6 with p-nitrobenzyl glyoxylate (toluene,

110°C, 1.5 h) afforded the hemiaminals 7 as a mixture of alcohol diastereomers. Treatment of 7 with thionyl chloride (THF,2,6-lutidine, -10°C, 0.3 h) gave the corresponding chlorides 8 which were converted to the phosphorane 9 with triphenylphosphine (dioxane, 2,6-lutidine, 1 h). The phosphorane 9 was cyclized in toluene (80°C, 17 h) to afford the bicyclic ester 10 in 41% overall yield from 6. The p-nitrobenzyl ester was conveniently removed by hydrogenolysis (5% Pd/C, 45 psi, MeOH-THF, 3.5 h) to afford the acid 11 in 82% yield. In contrast to penem 12, γ-lactam analogue 11 exhibited no antimicrobial activity or β-lactamase inhibition against a variety of organisms.



5 R = OCH_3
6 R = $SCOCH_3$

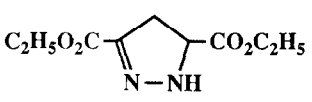
7 X = OH, Y = H
8 X = Cl, Y = H
9 X,Y = $P(C_6H_5)_3$

10 R = PNB
11 R = H

12

We next chose to prepare derivatives with a 2-aminothiazol-4-yl-methoximino-acetamido side chain at position 7, as these types of side chains are known to greatly enhance biological activity in many β-lactam systems.[9] It was felt that these derivatives might be particularly interesting in that the 6-acylamino penems are chemically too reactive for practical antibiotic activity.[10]

The pyrazoline 13, prepared in 82% yield from ethyl diazoacetate and ethyl acrylate,[11] was reductively cleaved with Raney nickel[12] (EtOH, 3500 psi, 60-115°C, 6 h) to afford a mixture of aminopyrrolidinones 14. Protection as the t-butyl carbamate 15 ($tBOC_2O$, CH_2Cl_2, 72 h) and saponification of the ester function (KOH, MeOH, 2 h) afforded a 63% yield of a mixture of isomeric acids 16. The acids 16 were converted to a mixture of acetates 17 with lead tetraacetate (THF, 67°C, 2 h). Exchange with thiolacetic acid to 18 followed by the standard Wittig sequence (as described above for the conversion of 6 → 10) afforded (after isomer separation by chromatography) a 4% yield of the cis bicyclic derivative 19 and a 15% yield of the trans derivative 20.[13] Ester removal (5% Pd/C, 45 psi, MeOH-THF), deblocking of the amine (TFA), and acylation with the HBT-active ester of 2-aminothiazol-4-yl-methoximino-acetic acid ($NaHCO_3$, acetone-H_2O) afforded the desired racemic γ-lactam analogues 21 and 22.



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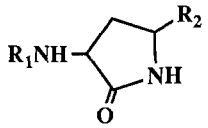


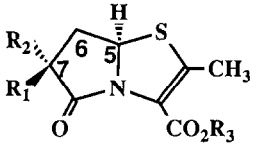
14 $R_1 = H$, $R_2 = CO_2C_2H_5$

15 $R_1 = tBOC$, $R_2 = CO_2C_2H_5$

16 $R_1 = tBOC$, $R_2 = CO_2H$

17 $R_1 = tBOC$, $R_2 = OCOCH_3$

18 $R_1 = tBOC$, $R_2 = SCOCH_3$

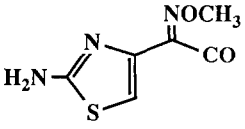


19 $R_1 = tBOCNH$, $R_2 = H$, $R_3 = PNB$

20 $R_1 = H$, $R_2 = tBOCNH$, $R_3 = PNB$

21 $R_1 = ATMONH$, $R_2 = R_3 = H$

22 $R_1 = H$, $R_2 = ATMONH$, $R_3 = H$

ATMO = 

Analogues 21 and 22 displayed low, yet demonstrable, levels of in vitro antibiotic activity against a wide variety of gram-positive and gram-negative organisms, e.g. the MIC of compound 22 against streptococcus pyogenes (C203) was 4 μg/ml.

These studies constitute an example of a γ-lactam system which exhibits antimicrobial activity. Further studies are under way to elucidate the mechanism of action of these derivatives and prepare analogues with greater activity. These results will be reported in due course.

Acknowledgments. We thank J. Westhead, M. Hoehn, and J. Ott for the biological studies and the physical chemistry department for providing analytical and spectral data. We gratefully acknowledge the work of J. Campbell and D. Vogt who performed the Raney nickel reaction, and D. Hunden who prepared large-scale amounts of compound 16. Finally, we thank L. Blaszczak and W. Scott for helpful discussions.

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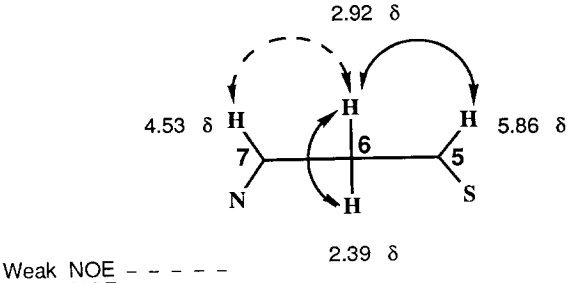
13. The relative configuration of H_5 and H_7 in isomers 19 and 20 was determined using difference NOE techniques as shown below:



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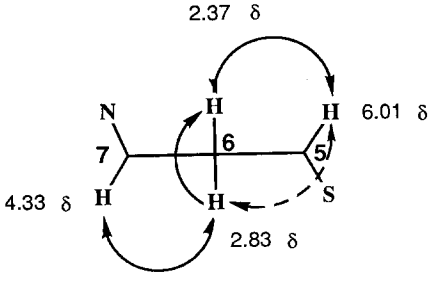

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