Tetrahedron Letters,Vol.28,No.3,pp 289-292,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

BICYCLIC PYRAZOLIDINONES, STERIC AND ELECTRONIC EFFECTS ON ANTIBACTERIAL ACTIVITY

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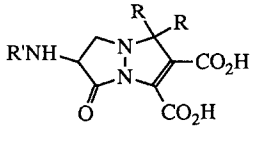
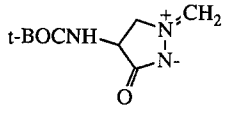
Summary: Bicyclic pyrazolidinones were synthesized as γ-lactam analogs of the β-lactam antibiotics. Several of these compounds exhibited broad spectrum in vitro antibacterial activity.

In the previous paper[1] we reported on the synthesis of bicyclic pyrazolidinones, e.g., 1. These constitute a new class of antibacterial agents based on the β-lactam model. We desired to replace the gem dimethyl moiety in 1 with hydrogen atoms, e.g., 2, in order to



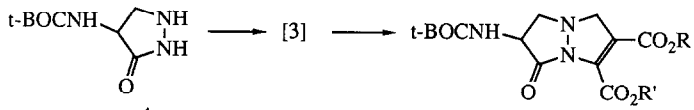
1 R=Me
2 R=H



3

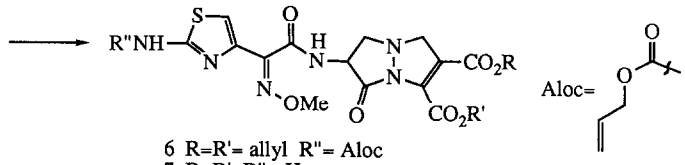
more closely mimic a typical β-lactam antibiotic. To prepare these compounds via a 1,3-dipolar cycloaddition route we required ylide 3. Previous attempts to synthesize unsubstituted azomethine imines of this type have resulted in the formation of dimeric species.[2] In certain instances azomethine imines have been generated and trapped in situ.[3]

We have found that treatment of pyrazolidinone 4[1] with aqueous formaldehyde in methanol gave rise to an amorphous solid which has not yet been fully characterized. Evidence for the ylide 3 (M^+=213) as well as a dimeric form (M^+=426) are found in its mass spectrum. Heating this material in the presence of diallyl acetylenedicarboxylate (CH_3CN, reflux, 2hr) provided the desired cycloadduct 5 in 49% yield.[4] This product is at least formally derived from the 1,3-dipolar cycloaddition of ylide 3 and the acetylene.



4

5 R=R'= allyl
8 R=Me R'= allyl
9 R= allyl R'=Me

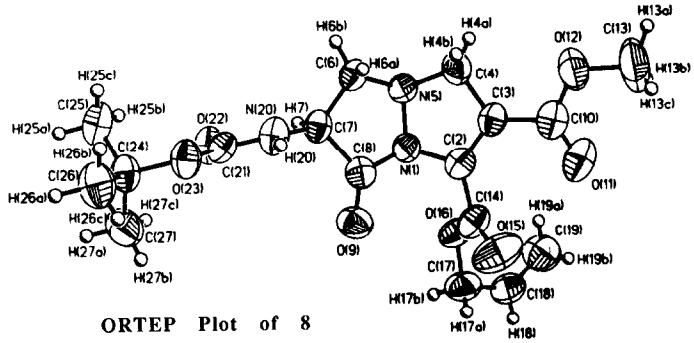


6 R=R'= allyl R"= Aloc
7 R=R'=R"= H
10 R= Me R'= allyl R"= Aloc
11 R= Me R'=R"= H

Deblocking of the amine (TFA), neutralization of the resulting salt with bistrimethylsilyltrifluoroacetamide, and acylation with the acid chloride of 2-allyloxycarbonyl aminothiazol-4-yl-methoximino-acetic acid (CH_2Cl_2-EtOAc) gave 6 in 59% yield. Palladium catalyzed cleavage of all three allyl protecting groups[5] was accomplished in one step ($(Ph_3P)_4Pd$, 3eq Bu_3SnH, acetone) to give 7. The in vitro antibacterial activity of 7 against a variety of gram positive and gram negative strains was enhanced relative to the gem-dimethyl analogs 1.[1]

By analogy to the corresponding cephalosporins[6], we reasoned an electron withdrawing ester substituent at the activating position, e.g., 11 might enhance the activity in this series relative to the carboxylate substituted 7.

The required allyl methyl acetylenedicarboxylate was prepared from allyl propiolate (1.$(Me_3Si)_2NLi$,THF,-78°;2. $ClCO_2Me$), in 26% yield. This was added to the mixture of 4 and formaldehyde (1,2-dichlorethane) under reflux to give a 1:1 mixture of cycloadducts 8 and 9. The regioisomers were separated by preparative HPLC. The more polar isomer (hexane-EtOAc 1:1) was shown to be the desired 8 by x-ray crystallography.[7]



ORTEP Plot of 8

Deblocking of the amine (TFA), neutralization of the resulting salt with bistrimethylsilyl-trifluoroacetamide, and acylation with the acid chloride of 2-allyloxycarboxyl-amino-thiazol-4-yl-methoximino acetic acid (CH_2Cl_2-EtOAc) gave 10 in 42% yield. Palladium catalyzed removal of the allyl ester and Aloc protecting groups completed the synthesis of 11.

Indeed, bicyclic pyrazolidinone 11 was found to exhibit broad spectrum antibacterial activity against a variety of gram positive and gram negative bacteria. For example, MICs vs. Strep. pyogenes (C203) = 4 μg/ml; Proteus rettgeri, (C24) = 1 μg/ml.

Studies to elucidate the mechanism of action of this exciting new class of compounds and prepare analogs with greater potency are underway. These results will be reported in due course.

Acknowledgements

We thank D. Preston and J. Ott for the biological evaluation of these compounds and the physical chemistry department for providing analytical and spectral data. We gratefully acknowledge P. Pranc for the large scale preparation of compound 4 and J. W. Fisher for compound 11. We also thank L. D. Hatfield, C. J. Barnett and Professor E. C. Taylor for helpful discussions.

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2) Dorn, H.; Zubek, A. Z. Chem. 1968, 7, 270. Dorn, H.; Ozegowski, R.; Radeglia, R. J. Prakt. Chem. 1977, 319, 177. Taylor, E. C.; Clemens, R.J.; Davies, H.M.L. J. Org. Chem. 1983, 48, 4567.

3) Grashey, R. In "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 1, p. 733.

4) Satisfactory spectral data were obtained for all new compounds.
Representative NMR spectral data:
Compound 5 (90 MHz, $CDCl_3$) δ 6.2-5.7, M, 2H; 5.52-5.0, M, 5H; 4.82, dm, 2H, J=6; 4.64, dm, 2H, J=6; 4.38, d, 1H, J=13; 4.04, t, 1H, J=8; 3.92, d, 1H, J=13; 2.88, dd, 1H, J=12, 8; 1.45, s, 9H.
Compound 7 (270 MHz, D_2O) δ 7.24, s, 1H; 5.25, m, 1H; 4.32, d, 1H, J=13; 4.20, m, 1H; 4.0, m, 1H; 4.08, s, 3H; 3.30, m, 1H.
Compound 8 (90 MHz, $CDCl_3$) δ 6.2-5.6, m, 1H; 5.5-5.04, m, 3H; 4.78, dm, 2H, J=5; 4.60, m, 1H; 4.4-3.7, m, 3H; 3.66, s, 3H; 2.83, dd, 1H J=12, 8; 1.36, s, 9H.
Compound 9 (90 MHz, $CDCl_3$) δ 6.1-5.6, m, 1H; 5.5-5.04, m, 3H; 4.70, m, 1H; 4.56, dm, 2H, J=5; 4.4-3.56, m, 3H; 3.84, s, 3H; 2.84, dd, 1H, J=12, 9; 1.36, s, 9H.
Compound 11 (270 MHz, D_2O) δ 7.08, s, 1H; 5.25, m, 1H; 4.30, d, 1H, J=11; 4.2-3.6, m, 2H; 4.02, s, 3H, 3.78, s, 3H; 3.28, t, 1H, J=8.

5) Jeffrey, P.D.; McCombie, S.W. J. Org. Chem. 1982, 47 587.

6) Kukolja, S.; Chauvette, R.R. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R.B.; Gorman, M. Eds.; Academic Press: New York, 1982; Vol. 1, p. 93.

7) Compound 8 crystallizes from benzene/hexane as yellow needles in the triclinic space group P 1 bar, with 2 molecules in a unit cell having the dimensions a = 9.373(3) A; b = 9.812(2) A; c = 11.334(3) A; alpha = 79.881(21)°; beta = 73.416 (25)°; gamma = 77.185 (23°) the calculated density was 1.310 g cm^{-3}. The intensities of 2804 unique refelctions with 2[theta] 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 direct methods routine SOLV 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 0.0584 for 1964 observed reflections.

(Received in USA 5 September 1986)