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BICYCLIC PYRAZOLIDINONES, A NEW CLASS OF ANTIBACTERIAL AGENT BASED ON THE β-LACTAM MODEL

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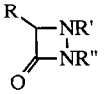
Summary: Several bicyclic pyrazolidinones were synthesized as γ-lactam analogs of the β-lactam antibiotics. Two of these compounds exhibited in vitro antibacterial activity, and thus constitute a new class of antibacterial agents.

The resurgence of interest in γ-lactam analogs of the β-lactam antibiotics prompts us to report our efforts in this area[1]. For some time now we have been interested in preparing γ-lactam analogs of the more recent classes of β-lactams to be discovered, namely the penems and carbapenems[2]. β-lactams are known to exert their activity by acylation of several specific enzymes, the penicillin binding proteins (PBP's), involved in bacterial cell wall synthesis[3]. We reasoned that a suitably substituted γ-lactam might also possess sufficient reactivity to react with these enzymes.

A third new type of highly reactive β-lactam is the aza-β-lactam 1 recently described by Taylor[4]. These compounds have proven to be especially unstable and attempts to prepare suitably elaborated bicyclic analogs, e.g. 2 have failed. This increased instability



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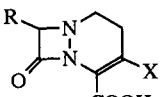

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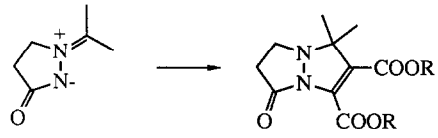
relative to the corresponding azetidinones suggested that the pyrazolidinone homolog e.g., 5 might provide the proper mixture of chemical stability and acylating ability to exhibit antimicrobial activity.

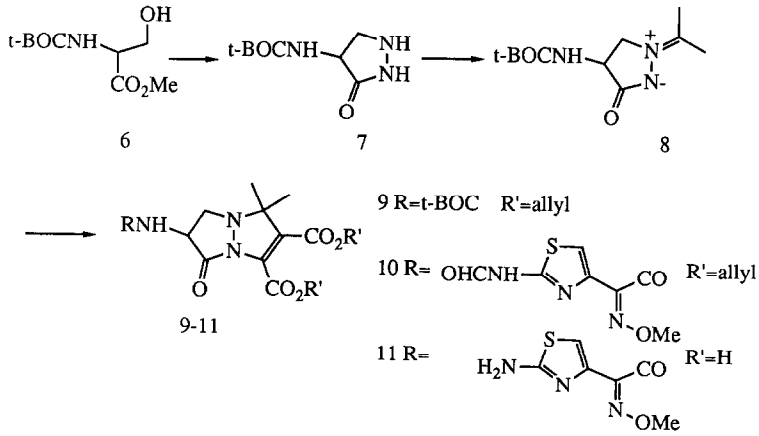
As an initial target we chose compound 5 which is readily available from the 1,3-dipolar cycloaddition of the known pyrazolidinium ylide 3[5] with diallyl acetylene dicarboxylate (CH_2Cl_2, RT, 72 hr)[6]. Palladium catalyzed deesterification[7] of 4 (6 mole % $(Ph_3P)_4Pd$, Bu_3SnH, acetone) gave the desired bis acid 5 in essentially quantitative yield.



3 4 R=allyl 5 R=H

We were delighted to find that 5 exhibited weak *in vitro* antimicrobial activity, e.g., vs. *Staph. aureus*.

Next, we turned our attention to the incorporation of an appropriate amide side chain, to more closely mimic the β-lactams. The required 4-amino-pyrazolidinone 7 was found to be readily available from D,L-serine. Thus, tosylation of the t-butyl carbamoyl-D,L-serine methyl ester 6, followed by treatment with hydrazine (CH_2Cl_2, RT, 16 hr), gave the desired pyrazolidinone 7 in 60% yield.



This was converted to the dimethyl ylide 8 by treatment with 2,2-dimethoxypropane and a trace of d-10-camphorsulfonic acid (MeOH, reflux, 1 hr, 100%). Cycloaddition with diallyl acetylene dicarboxylate (CH_2Cl_2, RT, 72 hr) gave the desired bicyclic pyrazolidinone nucleus 9 in 67% yield.

The t-BOC protecting group was removed (TFA) and the resulting amine salt treated with the acid chloride of 2-N-formylaminothiazol-4-yl-methoximino-acetic acid ($NaHCO_3$, acetone, H_2O) to give 10. Palladium catalyzed deesterification[7] (6 mole % $(Ph_3P)_4$ Pd, sodium-2-ethylhexanoate, acetone) followed by removal of the N-formyl protecting group (conc. HCl, MeOH) completed the synthesis of 11 in 32% yield from the nucleus 9.

Pyrazolidinone 11 displayed substantially increased in vitro antimicrobial activity vs. Staph. aureus. relative to 5. Further attempts to enhance the antimicrobial activity of these novel compounds are reported in the following paper.

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REFERENCES AND NOTES

1) Baldwin, J.E.; Chan, M.F.; Gallacher, G.; Monk, P.; Prout, K. J. Chem. Soc., Chem Commun. 1983, 250. Baldwin, J.E.; Chan, M.F.; Gallacher, G.; Otsuka, M.; Monk, P.; Prout, K. Tetrahedron 1984, 40, 4513. Baldwin, J.E.; Adlington, R.M.; Jones, R.H.; Schofield, C.J.; Zarocostas, C.; Greengrass, C.W. J. Chem. Soc., Chem. Commun. 1985, 194. Gordon, E. M.; Pluscec, J. Tetrahedron Lett. 1983, 24, 3419. During the course of this work a U.S. patent 4,428,960 (1984) appeared disclosing 3-amino-6-substituted thio-1-azabicyclo [3.2.0] hept-6-en-2-one-7-carboxylic acids as antibiotic substances. Chem. Abstr. 1984, 100, (23) 191655.

2) Boyd, D.B.; Elzey, T.K.; Hatfield, L.D.; Kinnick, M.D.; Morin, J.M. Tetrahedron Lett. 1986, 30, 3453. Boyd, D.B.; Foster, B.J.; Hatfield, L.D.; Hornback, W.J.; Jones, N.D.; Munroe, J.E.; Swartzendruber, J.K. ibid. 1986, 30, 3457. Baldwin, J.E.; Lowe, C.; Schofield, C.J.; Lee, E. ibid. 1986, 30, 3461.

3) Waxman, D.J.; Strominger, J.L. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R.B.; Gorman, M., Eds.; Academic Press: New York, 1982; Vol 3, p. 209.

4) Taylor, E.C.; Haley, N.F.; Clemens, R.J. J. Am. Chem. Soc. 1981, 103, 7743. Taylor, E.C.; Davies, H.M.L. J. Org. Chem. 1984, 49, 113. Taylor, E.C.; Davies, H.M.L. ibid. 1984, 49, 4415. Also see: Moody, C. J.; Pearson, C.J.; Lauton, G. Tetrahedron Lett. 1985, 26, 3167.

5) Dorn, H.; Otto, A. Chem Ber. 1968, 101, 3287. The cycloaddition of this ylide with dimethylacetylene dicarboxylate is also reported. Our attempts to prepare 5 by simple hydrolysis of the bis-methyl ester lead to decomposition of the bicyclic pyrazolidinone ring system.

6) Satisfactory spectral data were obtained for all new compounds.
Representative NMR spectral data:
Compound 7 (90 MHz, $CDCl_3$) δ 7.04, m, 1H; 5.12, m, 1H; 4.28, m, 1H; 3.94, m, 1H; 3.20, m, 1H; 1.45, s, 9H.
Compound 9 (270 MHz, $CDCl_3$) δ 5.90, m, 2H; 5.50-5.20, m, 4H; 5.10, m, 1H; 4.90-4.50, m, 5H, 3.74, m, 1H, 3.05, m, 1H; 1.52, s, 3H; 1.46, s, 9H; 1.32, s, 3H.
Compound 11 (90 MHz, D_2O) δ 7.08, s, 1H; 5.10, dd, 1H, J=12, 8; 3.99, s, 3H; 3.68, t, 1H, J=8; 3.38, t, 1H, J=12; 1.49 and 1.36, 2xS, 6H.

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

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