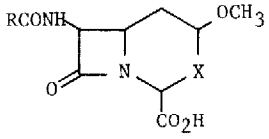
Tetrahedron Letters Vol. 21, pp 3947 - 3950 0040-4039/80/1008-3947$02.00/0

NUCLEAR ANALOGS OF β-LACTAM ANTIBIOTICS. 7[1].
THE SYNTHESIS OF 3-THIA- AND 3-AZA-1-DETHIACEPH-1-EM ESTERS

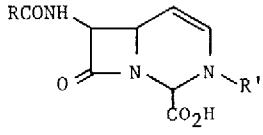
John G. Gleason*, Deborah Boles Bryan and Kenneth G. Holden
Research and Development Division
Smith Kline and French Laboratories
Philadelphia, Pennsylvania 19101

Summary: The total synthesis of a 3-thia- and a 3-aza-1-dethiacepham (9 and 16) are described. Neither compound possessed antibacterial activity vs B. subtilis. An unsaturated analog, a 3-aza-1-dethiaceph-1-em exhibited weak antibacterial activity.

In the course of our study of cephalosporins in which the heteroatom has been transposed to the 2 or 3 position, we observed unexpectedly high antibacterial activity for the 3-oxa-1-dethiacepham nucleus 1, and speculated that the fragmentation of the 1,3-oxazidine ring may play a role in activating the bicyclic β-lactam for antibacterial activity.[1,2] To further define the enhancement of biological activity by a 3-heteroatom, we have explored the synthesis of 3-thia- and 3-aza-1-dethiacephalosporins 2 and 3.

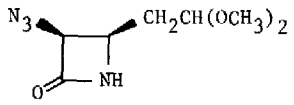


1, X = O
2, X = S

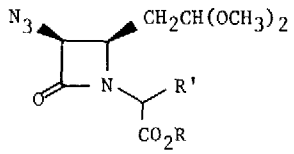


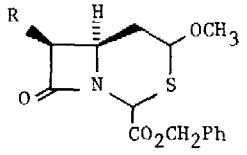
3

Thermal condensation of benzyl or methyl glyoxylate with cis-3-azido-2-(2,2-dimethoxyethyl)-azetidinone 4[1,3] afforded the carbinolamide 5a or 5b as mixture of diastereomers. Conversion of 5a to the more reactive chloride 6a ($SOCl_2$, pyridine) and reaction with potassium thioacetate gave thioester 7 in 50% yield from 4. Cyclization of 7 was effected under acid catalysis (BF_3.MeOH, rt) to afford the 3-thia-1-dethiacepham 8 in 13% yield[4]: IR (film) ν_{max} 2100 (azide), 1775 (β-lactam), 1740 (ester); NMR ($CDCl_3$) δ 2.2 (m, C-1H_2), 3.15 (s, OCH_3), 4.25 (m, C-6H), 4.65 (dd, $J_{1,2}$ = 3, 3.5 Hz, C-2H), 4.85 (d, $J_{6,7}$ = 5Hz, C-7H) 5.15 (s, CH_2Ph), 5.18 (s, C-4H), 7.35 (m, Ph); MS(EI) m/e 320 ($M^+ - N_2$), 288, 266, 213, 185, 91.



4





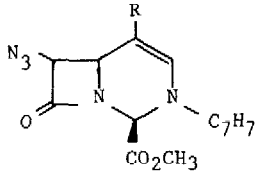
8, R = N_3
9, R = R = PhCHCONH
OCHO

5a R= CH_2Ph, R'= OH
5b R= CH_3, R'=OH
6a R= CH_2Ph, R'= Cl
6b R= CH_3, R'= Cl
7 R= CH_2Ph, R'= $SCOCH_3$
10a R= CH_3, R'= β-$NHC_6H_4pCH_3$
10b R= CH_3, R'= α-$NHC_6H_4pCH_3$

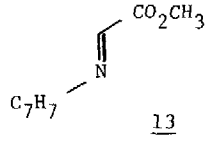
Reduction of the azide (PtO_2, 1 atm H_2, EtOAc, 1 hr) and acylation with formyl mandeloyl chloride gave the amide 9 IR (nujol) 1760 (β-lactam), MS (FD) m/e 484. This compound was inactive at 1000 μg/ml vs B. subtilis[5].

To prepare a 3-aza analog, a similar approach was employed. Addition of toluidine to the chloride 5a gave a mixture of diastereomeric amines 10, separable by chromatography (stereochemical assignments for 10a and 10b were inferred from their respective cyclization products and are tenative).

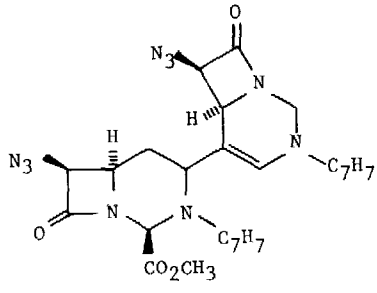
Attempts to effect cyclization of the less polar amine 10a were not encouraging. At elevated temperature in the presence of pTSA, the bicyclic product 11 was obtained. This product presumably arises from condensation of the initially formed 12 with acylimine 13, a potential degradation product of 10a. The use of BF_3 permitted cyclization under much milder conditions, however the dimeric β-lactam 14 was the sole isolable product. While both experiments argue for the intermediacy of 12, its presence was never detected.



11, R = $CH(NHC_7H_7)CO_2CH_3$
12, R = H

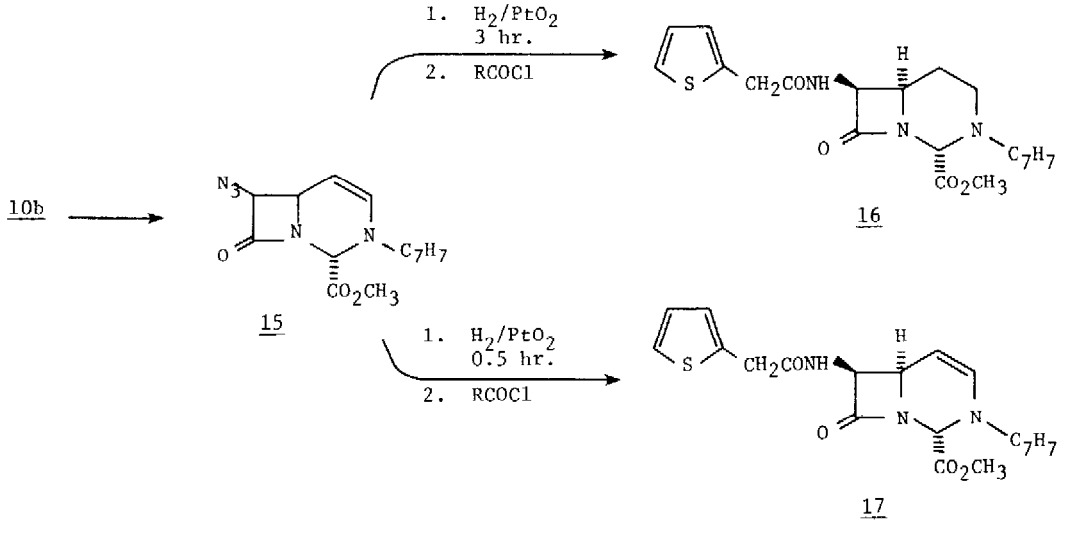


13



14

In contrast, the cyclization of 10b proceeded smoothly under mild acid catalysis to afford the bicyclic 3-aza-1-dethiaceph-1-em ester 15 in 70% yield: IR (film) ν_{max} 2110 (azide), 1780 (β-lactam), 1750 (ester), 1635 (eneamine); UV (EtOH) λ_{max} 270 nm; NMR ($CDCl_3$) δ 2.2 (s, C_6H_4-CH_3), 3.7 (s, CO_2CH_3), 4.18 (dd, $J_{1,6}$=1.5 Hz, $J_{6,7}$=5Hz C-6H), 4.5 (d, C-7H), 4.78 (dd, $J_{1,2}$=10.5 Hz, C-1H), 5.55 (s, C-4H), 6.45 (d, C-2H), 7.2 - 6.3 (q, C_6H_4); MS(EI) m/e 313 (M^+). The configuration of the carboxyl group of 15 was tentatively assigned as depicted on the basis of an observed 0.5 ppm downfield shift of the nmr resonance of the C-4 proton of 15 relative to the bicyclic products 11 and 14 obtained from the cyclization of the opposite diastereomer 10a. Catalytic reduction (PtO_2, 3 hr, rt) of 15 effected reduction of the azide and saturation of the enamine to give, after acylation with thienylacetyl chloride, the 3-aza-1-dethiacepham 16, (IR (film) ν_{max} 1780 (β-lactam), 1750 (ester); NMR ($CDCl_3$) δ 2.25 (s, $C_4H_6CH_3$), 3.7 (s, CO_2CH_3) 3.8 (s, CH_2CONH), 3.3-4:25 (m, C-1,2,6-H), 5.2 (dd, C-7H), 5.73 (s, C-4H), 6.2-5.8 (br, NH), 7.3-6.7 (m, C_6H_4, C_4H_3S); MS (FD) m/e 413). Selective reduction of the azide (PtO_2, 0.5 hr, rt) afforded after acylation the 3-aza-1-dethiaceph-1-em 17: IR (film) ν_{max} 1780 (β-lactam), 1750 (ester), 1690 (amide), 1664 (enamine); UV (EtOH) λ_{max} 268, 241 nm; NMR ($CDCl_3$) δ 2.3 (s, $C_6H_4CH_3$), 3.75 (s, CO_2CH_3), 3.8 (s, CH_2CON), 4.3 (dd, $J_{1,6}$=2Hz, $J_{6,7}$=5.5Hz, C-6H), 4.55 (dd, C-1H), 5.4 (dd, C-7H), 5.7 (s, C-4H), 5.9 (d, J=8.5Hz, NH), 6.5 (d, $J_{1,2}$=10Hz, C-2H), 7.2-6.6 (m, C_4H_3S, C_6H_4); MS (FD) m/e 411.1236 (calc'd for $C_{19}H_{20}N_3O_4S$, 411.1252).



The 3-aza-1-dethiaceph-1-em ester 17 possessed very weak antibacterial activity against B. subtilis at 1000 μg/ml[5], while the saturated ester 16, like the 3-thia-1-dethia cepham 9, was inactive at this concentration. In contrast, the corresponding 3-oxa-1-dethiacepham esters of 1 generally exhibited significant activity in the 50-500 μg/ml range.[1,6] The lack of significant biological activity for 16 and 17 may reflect the relatively poor ability of the 3-aza nitrogen to participate in the cleavage of the β-lactam bond.[8]

References

1. For part 6 in this series, see J. G. Gleason, T. F. Buckley, Kenneth G. Holden, D. B. Bryan and P. Dandridge, J. Amer. Chem. Soc., 101, 4730 (1979).

2. D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman and J. G. Gleason, J. Amer. Chem. Soc., 99, 2353 (1977).

3. Satisfactory spectral data (ir, nmr and ms) and/or elemental analyses were obtained for all compounds.

4. A single isomer was formed on cyclization of the diastereomeric mixture 7. Although comparison with other similar β-lactam systems would suggest the β-configuration at C-2, no definitive stereochemical assignment could be made.

5. A disc assay with cephaloridine (10 μg/ml) as a standard was used for comparison of synthetic β-lactam products.

6. Such shifts in the C-4 proton resonance have been observed in a number of analogous bicyclic β-lactam systems[1,7] and have been suggested as diagnostic of relative stereochemistry at C-4.[7]

7. E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate and P. Tolliday, J. Chem. Soc., Perkin Trans. I, 2479 (1977).

8. Other nitrogen containing bicyclic β-lactams have been described, however none have demonstrated significant biological activity. See, for example, J. Finkelstein, K. G. Holden, R. Sneed and C. D. Perchonock, Tetrahedron Letters, 1977, 1855; T. W. Doyle, B. Y. Luh, D. T. Chu, and B. Belleau, Can. J. Chem., 55, 2719 (1977). For a review of the synthesis and antibacterial activity of nuclear analogs of β-lactams antibioties see K. G. Holden, J. G. Gleason and W. F. Huffman, and C. D. Perchonock, in "Drug Action and Design: Mechanism-Based Enzyme Inhibitors", (T. Kalman, ed.) Elsevier North-Holland, NY, 1979.

(Received in USA 9 May 1980)