Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5601-5604, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01135-5

Synthesis of Reactive γ-Lactams Related to Penicillins and Cephalosporins

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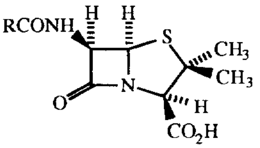
Abstract : Gamma lactam analogues based on the penicillin and cephalosporin framework have been synthesised which, in keeping with their design as potential inhibitors of bacterial cell wall biosynthesis, show high reactivity towards modest nucleophiles. An X-ray crystal structure of one of these compounds allows structural comparisons to be made with classical β-lactam antibiotics.

The antibacterial effect of β-lactam antibiotics such as penicillins (**1**) and cephalosporins (**2**) is due to their capacity to disrupt bacterial cell wall biosynthesis. This is achieved by inhibiting penicillin binding proteins (PBPs) which are membrane bound serine peptidases. These recognise *D*-alanyl-*D*-alanine peptide termini and the structural and conformational similarity of the antibiotics to these natural substrates is believed to ensure their acceptance by the PBPs. The reactivity of the fused β-lactam ring then results in the formation of a covalent PBP-inhibitor complex which prevents the PBPs from taking further part in bacterial cell wall synthesis.



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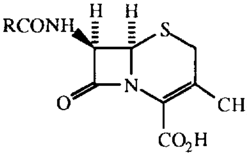

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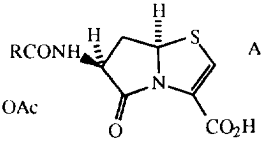

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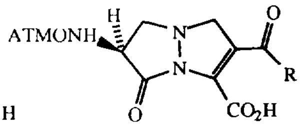

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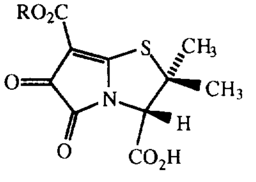
The extensive use of classical β-lactam antibiotics such as penicillin in medicine has given rise to an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer, and so there has been much effort expended in recent years to prepare new structural types which will both target the PBPs and overcome the defence mechanisms of the bacteria.[1] In an attempt to move away from the β-lactam motif, several research groups have investigated the synthesis of non-β-lactam compounds, and γ-lactams and their analogues have proved popular targets.[1,2] In 1986, Baldwin *et al.*[3] prepared the compounds (**3**) which were γ-lactam analogues of the 6-acylaminopenems which had been prepared by Woodward[4] but which were considered to be too reactive for practical use as anti-bacterial compounds. The γ-lactam analogues (**3**) had weak but real antibacterial activity against both Gram positive and Gram negative organisms. Pyrazolidinone-containing compounds such as the carbapenem analogues (**4**) prepared by the Eli Lilly group[5] have been proven to bind to bacterial PBPs[6] and to have useful *in vitro*[7] and *in vivo*[8] antibacterial properties.

In a search for γ-lactams which would resemble the classical β-lactam antibiotics enough to be accepted by PBPs and which would have a reactive amide ring, we selected compounds of the general type **(5)** and **(6)** as targets. These would structurally resemble penicillins and cephalosporins and the vinylogous urethane/amide properties provided by the conjugated system in the five-membered ring would compete for the lone pair on nitrogen of the lactam ring. This should make the lactam carbonyl group more electrophilic. An additional destabilising feature would be the Coulombic interaction in the *cis* α-dicarbonyl system in the compounds.



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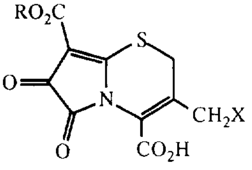
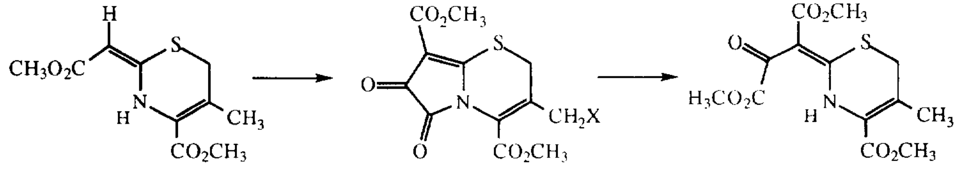


(6)

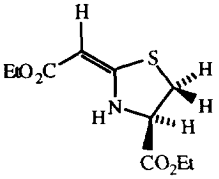
Since we had prepared the thiazine (7)[9] and used it in a combined Michael / cyclisation reaction to prepare six-six and six-seven fused bicyclic compounds, it was appropriate to attempt to prepare a compound related to **(6)** above using this compound. Treatment of the thiazine (7) with oxalic acid under the phosphazo coupling conditions which had proved successful in our earlier studies[9] met with failure but when the thiazine was reacted with one equivalent of oxalyl chloride in methylene chloride containing triethylamine, a 63% yield of a solid, $C_{12}H_{11}NO_6S$, m. p. 196 - 198 °C, was obtained. There were four separate carbonyl absorptions in the IR spectrum at 1768, 1736, 1703 and 1659 cm^{-1} and in the ^{13}C NMR spectrum at 161, 162, 172 and 181 ppm. The UV spectrum (λ_{max} 243, 273, 318 and 427 nm) was considerably shifted from that of the starting thiazine **(7)** (λ_{max} 224, 281 and 336 nm). These data were in keeping with the product being the desired bicyclic γ-lactam **(8)** and its lability was evident from the fact that, when it was warmed in methanol for ten minutes, the compound reacted to give the methanol adduct, $C_{13}H_{15}NO_7S$, m.p. 143 - 145 °C, λ_{max} 230 and 353 nm. The ^1H- and ^{13}C-NMR spectra indicated that this was a mixture of the thiazine **(9)** and its geometric isomer.



(7) (8) (9)

We had therefore succeeded in synthesising an extremely labile γ-lactam **(8)** with structural similarity to a cephalosporin antibiotic. It had no antibacterial properties as measured by an agar dilution method using surface inoculation of bacteria but, since it was an ester, this was not surprising. Various attempts to prepare the free acid from the methyl ester were unsuccessful due to the lability of the ring system and even when the allyl ester was prepared, we were unable to access the free acid using $Pd(PPh_3)_4$ catalyst.[10]

To obtain a thiazolidine analogue of our reactive γ-lactam, we now reacted the thiazolidine **(10)**[9] with oxalyl chloride as before and obtained the product **(11)** as an orange gum in 56 % yield. This had the expected ^1H- and ^{13}C-NMR spectra, ν_{max} 1771, 1738, 1733 and 1683 cm^{-1} and λ_{max} 243, 286 and 382 nm. The free acid of the penicillin analogue **(13)** was finally prepared by first synthesising ethoxycarbonylacetimino ethyl ether hydrochloride from ethyl cyanoacetate[9] and reacting it with D-penicillamine hydrochloride to yield the thiazolidine free acid **(12)**. This was then reacted with oxalyl chloride to give the penicillin analogue **(13)**. This free acid still had no useful antibacterial properties using the above agar dilution method.



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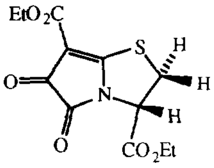

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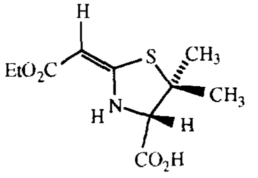

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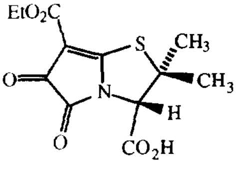

(13)

Having synthesised the compounds (**8**), (**11**) and (**13**) and shown that compound (**8**) was a reactive amide, we now wished to compare the relative rates of reaction of these compounds. This was achieved by measuring the disappearance of the absorbance at high λ_{max} with time on dissolution in methanol at room temperature. The results indicated a half life for the thiazine (**8**) of 25 min whereas the thiazolidine (**11**) had a half life of 70 min. The free acid (**13**) was more reactive, with a half life of 35 min.

In an early attempt to assess the relationship between antibacterial activity and overall structure as determined by X-ray crystallography[11] an early suggestion by Woodward[12] that biological activity could be ascribed to hindered amide resonance seemed to be confirmed since active compounds had an amide nitrogen with significant pyramidal character and a longer C-N bond and a shorter C-O bond than a normal amide. Later studies by Cohen[13] and Ghuysen[14] indicated that the need for the antibacterial compound to fit the target active site was paramount for activity. We have therefore recrystallised the γ-lactam (**8**) from benzene and determined its structure by X-ray analysis. The structure is shown in Figure 1a from the β-face and in Figure 1b from along the axis of the γ-lactam ring.[15]

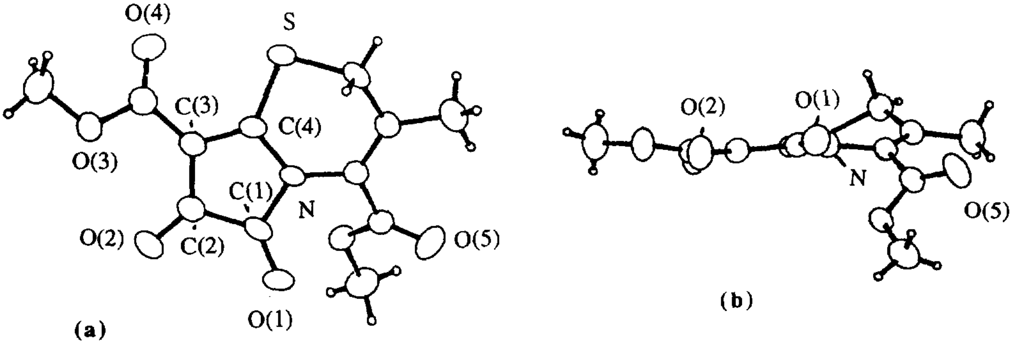

Figure 1 : Structure of the γ-lactam (**8**) determined by single crystal X-ray diffraction.
(**a**) viewed from the β-face of the molecule;
(**b**) viewed along the axis of the γ-lactam ring

Cohen[13] noted that the more active compounds in his study had their carboxyl group closer to the β-lactam amide with a separation distance between the oxygen atom of the amide group and the carbon atom of the carboxylate group of 3.0 - 3.9 Å compared to more than 4.1 Å in inactive compounds. This distance was found to be 2.89 Å in our compound. In view of the suggested relationship between the non-planarity of the amide nitrogen in β- and γ-lactams and biological activity, it is of interest that the amide nitrogen in our compound is nearly planar (sum of the angles at nitrogen is 359.4°). The S-C(4) bond [1.705 (3) Å] adjacent to the C(3)-C(4) double bond is significantly shorter than the S-C(5) bond [1.820 (4) Å]. Also the C(2)-O(2) bond [1.215 (4) Å] is slightly longer and the C(2)-C(3) bond [1.436 (5) Å] slightly shorter than normal, perhaps indicating some delocalisation extending from O(2) to S. The C(1)-O(1) bond [1.201 (4) Å] is normal. Superimposing our structure on the structure[16] of cephaloridine showed good overlay for amide and carboxyl groups but not for the sulfur atoms.

Acknowledgements :

We thank the E.P.S.R.C. and Zeneca Pharmaceuticals PLC for a CASE studentship (to D.L.).

References and Notes

1. Marchand-Brynaert, J.; Ghosez, L., 'Recent Progress in the Chemical Synthesis of Antibiotics', Lukas, G.; Ohno, M. eds., Springer-Verlag, Berlin, 1990, pp. 727 - 794.
2. Baldwin, J. E.; Lynch, G. P.; Pitlik, J., *J. Antibiotics*, 1991, **44**, 1 - 24.
3. Baldwin, J. E.; Lowe, C.; Schofield, C. J., *Tetrahedron Lett.*, 1986, **27**, 3461 - 3464.
4. (a) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B., *J. Am. Chem. Soc.*, 1980, **102**, 2039 - 2043; (b) Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B., *J. Am. Chem. Soc.*, 1978, **100**, 8214 - 8222; (c) Lang, M.; Prasad, K.; Holick, W.; Gosteli, J.; Woodward, R. B., *J. Am. Chem. Soc.*, 1979 **101**, 6296 - 6301; (d) Ernest, I.; Gosteli, J.; Woodward, R. B., *J. Am. Chem. Soc.*, 1979, **101**, 6301 - 6305.
5. (a) Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W., *Tetrahedron. Lett.*, 1987, **28**, 285 - 288; (b) Jungheim, L. N.; Sigmund, S. K.; Jones, N. D.; Swartzendruber, J. K., *Tetrahedron Lett.*, 1987, **28**, 289 - 292: (c) Jungheim, L. N.; Sigmund, S. K., *J. Org. Chem.*, 1987, **52**, 4007 - 4013: (d) Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepherd, T. A.; Sigmund, S. K., *Tetrahedron,* 1988, **44**, 3119 - 3126: (e) Holmes, R. E.; Neel, D. A., *Tetrahedron Lett.*, 1990, **31**, 5567 - 5570.
6. Allen, N. E.; Hobbs, J. N.; Preston, D. A.; Turner, J. R.; Wu, C. Y. E., *J. Antibiotics*, 1990, **43**, 92 - 99.
7. Jungheim, L. N.; Holmes, R. E.; Ott, J. L.; Teransky, R. J.; Draheim, S. E.; Neel, D. A.; Sigmund, S. K.; Shepherd, T. A., *XXVI Interscience Conf. on Antimicrobial Agents and Chemotherapy,* 1986, Abstr. 601.
8. Preston, D. A.; Counter, F. T.; Felty-Duckworth, A. M.; Turner, J. R., *XXVI Interscience Conf. on Antimicrobial Agents and Chemotherapy*, 1986, Abstr. 603.
9. Capps, N. K.; Davies, G. M.; Loakes, D.; McCabe, R. W.; Young, D. W., *J. Chem. Soc., Perkin Trans. 1,* 1991, 3077 - 3086.
10. We thank Dr S. Bhattia for the experiments with the allyl ester.
11. Sweet, R. M.; Dahl, L. F., *J. Am. Chem. Soc.*, 1970, **92**, 5489 - 5507.
12. Johnson, J. R.; Woodward, R. B.; Robinson, R in "The Chemistry of Penicillin", Clarke, H. T.; Johnson, J. R.; Robinson, R. eds., Princeton University Press, Princeton, N.J., 1949, pp. 440 - 454.
13. Cohen, N. C., *J. Med. Chem.*, 1983, **26**, 259 - 264.
14. Lamotte, J.; Dive, G.; Ghuysen, J. M., *Eur. J. Med. Chem.*, 1991, **26**, 43 - 50.
15. **Crystal data:** $C_{12}H_{11}NO_6S$, M = 297.3, monoclinic, space group $P2_1/c$ (No. 14), a = 8.193 (2), b = 21.892 (4), c = 8.241 (3) Å, β = 117.32 (3) °, U = 1313.1 Å^3, Z = 4, D_c = 1.50 g cm^{-3}, Mo-Kα (monochromator), λ = 0.71069 Å, μ = 2.6 cm^{-1}. Crystal size 0.5 x 0.3 x 0.05 mm^3. Enraf-Nonius CAD4 diffractometer, 2550 unique reflections for $2 < \theta < 25$ °, 1506 reflections with $I > \sigma(I)$ used in the refinement, R = 0.047, R' = 0.052. H atoms located and refined isotropically. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).
16. Boles, M. O.; Girven, R. J., *Acta Cryst.*, 1976, **B32**, 2279 - 2284.

† These compounds had the expected analytical and spectroscopic data.

(*Received in UK* 15 *May* 1996; *revised* 5 *June* 1996; *accepted* 7 *June* 1996)