Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2333-2336, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

Structural Studies of Ritipenem Acoxil (FCE 22891). X-Ray Crystal Structure and Chiroptical Properties.

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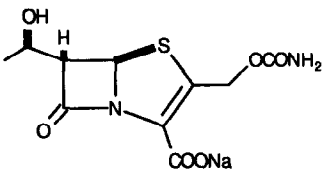
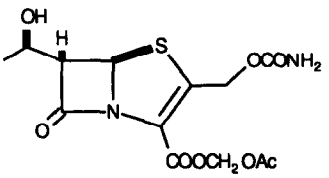
(*Received* 1 *April* 1993)

Abstract. The structure of Ritipenem Acoxil, obtained by single crystal x-ray diffraction analysis, is reported and some stereochemical features are discussed. The compound exhibits a characteristic CD spectrum. The relevance of the C-5 configuration in the determination of the sign of the CD bands is also discussed.

Penems are a novel class of synthetic β-lactam antibiotics conceptually created under the guidance of Nature; in fact, although devoid of natural equivalents, they were originally devised by the late Professor Woodward as nuclear hybrids of penicillins and cephalosporins, containing the bicyclic ring of the former and the conjugate double bond of the latter. Subsequently, the revelation of the naturally occurring carba-analogue thienamycin was the turning point in the penem research suggesting to synthetic chemists the introduction of its peculiar 6-hydroxyethyl side-chain in the penem skeleton; this gave rise to a new family of antibiotics which have elicited great interest due to the peculiar set of antibacterial properties and to the challenge posed by their synthesis. Among numerous penem derivatives synthesized in our laboratories, FCE 22101 (**1**) and FCE 22891 (**2**)[1] have been selected for clinical development as injectable and oral drugs, respectively. In this paper the single crystal X-ray analysis and the CD spectrum of **2** are reported and discussed.



1



2

Crystals of **2**, acetoxymethyl (5R, 6S)-2-carbamoyloxymethyl-6-(1R)-hydroxyethyl-2-penem-3-carboxylate, which were suitable for single-crystal X-ray diffraction work, were grown from *n*-hexane/$CHCl_3$. Incidentally, this is the first example of crystal structure of a *per se* biologically active 6-hydroxyethyl penem.

Table 1 - Bond distances (Å) for non-H atoms, uncorrected and corrected for riding motion (average e.s.d. = 0.02 Å).

Bond		corrected	Bond		corrected
S1-C2	1.74	1.75	C9-O10	1.45	1.49
S1-C5	1.84	1.84	C9-C11	1.49	1.51
C2-C3	1.38	1.38	C12-O13	1.44	1.46
C2-C12	1.46	1.47	O13-C14	1.37	1.38
C3-N4	1.41	1.42	C14-O15	1.23	1.25
C3-C17	1.42	1.43	C14-N16	1.31	1.32
N4-C5	1.47	1.49	C17-O18	1.22	1.23
N4-C7	1.37	1.37	C17-O19	1.32	1.33
C5-C6	1.51	1.51	O19-C20	1.43	1.43
C6-C7	1.54	1.54	C20-O21	1.54	1.60
C6-C9	1.51	1.53	O21-C22	1.59	1.62
C7-O8	1.24	1.26	C22-C23	1.90	1.91

Table 2 - Bond angles (°) for non-H atoms. The average e.s.d. is 1.5°.

Angle		Angle	
C2-S1-C5	91	N4-C7-C6	93
S1-C2-C12	121	C6-C7-O8	134
S1-C2-C3	115	N4-C7-O8	132
C3-C2-C12	124	C6-C9-C11	113
C2-C3-C17	126	C6-C9-O10	106
C2-C3-N4	111	O10-C9-C11	111
N4-C3-C17	122	C2-C12-O13	109
C3-N4-C7	128	C12-O13-C14	119
C3-N4-C5	115	O13-C14-N13	113
C5-N4-C7	92	O13-C14-O15	121
S1-C5-N4	105	O15-C14-N16	125
N4-C5-C6	91	C3-C17-O19	114
S1-C5-C7	117	C3-C17-O18	122
S1-C5-C6	119	O18-C17-O19	124
C5-C6-C9	117	C17-O19-C20	118
C5-C6-C7	84	O19-C20-O21	108
C7-C6-C9	116	C20-O21-C22	96

X-ray diffraction analysis showed monoclinic symmetry, space group $P2_1$ (a = 16.402(3) Å, b = 4.985(1) Å, c = 10.330(2) Å; β = 97.95(3)°; V = 836.5 Å^3; Z = 2; D_c = 2.9 g/cm^3; μ = 4.50 cm^{-1}).[2] Refinement of the anisotropic atomic displacement parameters has been performed only for non-H atoms; the positions of the H atoms were calculated at convergence with program PARST,[3] inserted with an overall isotropic temperature factor equal to 4 Å^2 but not refined. At convergence, R_{all} = 10.6%, R_{obs} = 8.0%, S = 1.63; secondary extinction = $6.82 \cdot 10^{-5}$; scale factor = 2.557.

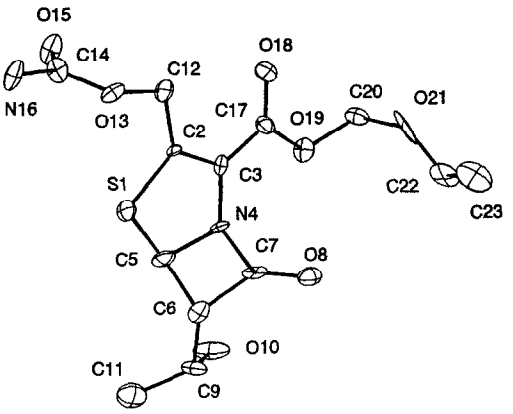


Figure 1 - ORTEP[4] perspective drawing of FCE 22891.

Relevant disorder is present for the acetate group (atoms O21-O24) and prevents determination of coordinates for O24, which is bonded to C22, from the difference Fourier maps. An attempt of obtaining better coordinates for these atoms on the basis of energy calculations was made, but the results did not lower the final R factors. Bond distances and bond angles are given in Tables 1 and 2; positional and displacement parameters have been deposited at the Cambridge Crystallographic Data centre; the molecular structure and the atomic numbering are shown in Figure 1. The angle between the least squares planes through the ring [S1, C2, C3, N4, C5] and

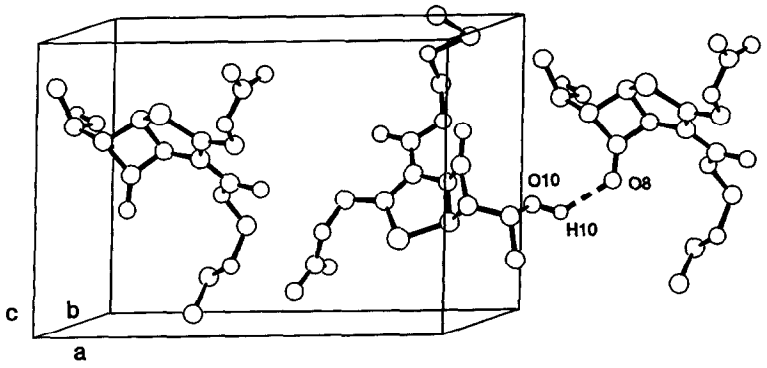


Figure 2. SCHAKAL[5] drawing of the unit-cell content. Intermolecular hydrogen bonding is shown.

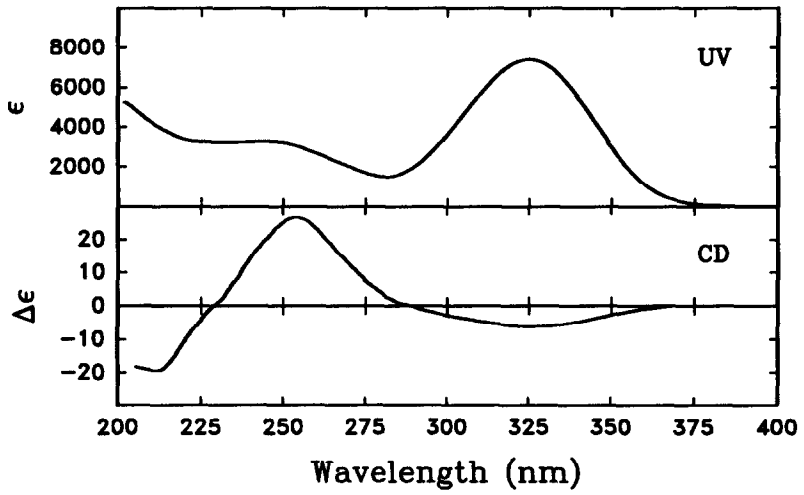


Figure 3. UV and CD spectra of FCE 22891 dissolved in ethanol (c = $6.6 \cdot 10^{-4}$ M, pathlength 0.2 cm).

[N4, C5, C6, C7] is 54.5°. This value is very similar to those reported for other penem derivatives (from 53.9° to 56.5°).[6] The values of bond distances and bond angles are also comparable, within e.s.d., with the exception of the C2-C3 bond, (Table 1) which is slightly longer then those of the literature compounds (in the range 1.33-1.36 Å); on the contrary, the N4-C7 bond is correspondingly shorter (literature values 1.40-1.41 Å). Interestingly, the hydroxyl group O10 is directed far away from the β-lactam carbonyl oxygen, (O8-O10 = 3.49 Å) thus suggesting the absence of an intramolecular hydrogen bonding.[7] However, a partial intermolecular hydrogen bonding between O8 and O10 is present in the crystal (O8-O10 = 2.88 Å; O8-H10 = 2.09 Å) and helps to

stabilize the molecular packing (Figure 2). The β-lactam ring exhibits a puckered conformation with the distance *r* of O8 from the plane N4-C5-C6 of 0.37 Å; the bond S1-C5 is almost orthogonal to the β-lactam plane (distance of S1 from the plane = 1.53 Å, bond length S1-C5 = 1.84 Å).

The absorption spectrum of penems (Figure 3) displays a characteristic band above 300 nm, which is not observed in the spectra of cephalosporins or penicillins.[8] This band, which is interpretable as a charge transfer transition involving sulphur and the aminoacryl chromophore, gives rise to a negative Cotton effect in the CD spectrum of FCE 22891 (Figure 3). Two other Cotton effects, positive at 260 nm and negative below 220 nm, strongly mimic those of 3-cephem compounds[9] at 260 and 230 nm, respectively. However, in the absence of a detailed theoretical study of the penem chromophore, this correspondence must be considered as hypothetical. Interestingly, the qualitative shape of the CD spectrum of penems (sign and band location) is preserved in Δ^4-thiazolines deriving from hydrolytic cleavage of β-lactam bond.[10] This latter observation confirms location of the chromophore in the thiazoline ring and consistently indicates predominance of C-5 chiral centre in the determination of the signs of CD bands.

References and notes.

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2. X-ray single crystal analysis and data collection were performed on a Philips PW1100 four-circle diffractometer (monochromatic MoKα radiation, λ = 0.7107 Å) and unit-cell dimension calculated by least-squares refinement of 25 rows in the θ range 2-20; before data collection, the set of the crystallographic axes was checked to be right-handed. This implies that the reported one is the absolute configuration of FCE 22891. Two monoclinic equivalent sets of reflections (hkl and $h\bar{k}l$) were measured in the θ range 2-20°, yielding 1550 independent reflections, corrected for absorption (max.= 1.04) and merged (R_{sym}= 2.8% for the 941 independent reflections). The structure has been solved by direct methods (MULTAN 80: Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. University of York, England, and University of Louvain, Belgium, 1980). Full-matrix least-squares F-refinement on the 726 reflections with $I \geq 3\sigma(I)$ was performed with a locally rewritten version of the program ORFLS: Busing, W. R.; Martin, K. O.; Levy, H. A.; ORFLS, Report ORNL-TM 305, Oak Ridge National Laboratory, Oak Ridge TN, USA 1962. Scattering factors for neutral atoms were obtained from International Tables for X-ray Crystallography, vol. IV, Kynoch Press, Birmingham, 1974.
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