The results of this refinement are: number of refined parameters p = 315, number of reflections used in the LS refinement n = 4035, wR_2 = 0.2711 for 4035 reflections, S = $[\Sigma w(F_o^2 - F_c^2)/(p - n)]^{1/2}$ = 0.746, w = $1/[\sigma^2(F_o^2) + (0.1658 P)^2]$ where P = $1/3[\max.(F_o^2,0) + 2F_c^2]$, $wR_{2'}$ = 0.2796 for all 4062 reflections (27 reflections with Δ/σ > 4 omitted in the refinement), R_1 = 0.0924 for 1267 F_o > $4\sigma(F_o)$, $R_{1'}$ = 0.2011 for all data, S = $[\Sigma w(F_o - F_c)^2/(p - n)]^{1/2}$ = 0.827 where wR_2 = $[\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, R_1 = $\Sigma |F_o - F_c| /\Sigma F_o$. A comparison of the structural parameters (coordinates, displacement parameters, bond distances, angles, etc.) from the two refinements shows that, as a result of the increased number of observations, the e.s.d.'s are much lower ($\sim 1/3$) for the F_o^2 refinement but that differences between bond distances and angles are not significant, which supports the view that the quality of intensity data is much more important than the amount of data. Half-normal probability plots and a table of the distances and angles obtained from the F_o^2 refinement have been deposited.

References

Amlaiky, N., Leclerc, J., Decker, N. & Schwartz, J. (1983). *Eur. J. Med. Chem. Chim. Theor.* **18**, 437-439.

Belletti, D., Ugozzoli, F., Cantoni, A. & Pasquinelli, G. (1979). *Gestione on Line di Diffrattometro a Cristallo Singolo Siemens-AED con Sistema General Automation Jumbo* 220. Internal Report 1- 3/79. Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma, Italy.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354-1358.

Jamart-Grégoire, B., Caubère, P., Blanc, M., Gnassounou, J. P. & Advenier, C. (1989). *J. Med. Chem.* **32**, 315-320.

Johnson, C. K. (1965). *ORTEP.* Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Lawton, S. L. & Jacobson, R. A. (1965). *The Reduced Cell and its Crystallographic Applications.* Ames Laboratory. Available from the Clearinghouse for Federal Scientific and Technical Information, National Bureau of Standards, US Department of Commerce, Springfield, Virginia, USA.

Lehmann, M. S. & Larsen, F. K. (1974). *Acta Cryst.* A**30**, 580-589.

Le Page, Y. (1987). *J. Appl. Cryst.* A**20**, 264-269.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Motherwell, W. D. S. & Clegg, W. (1978). *PLUTO.* Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

Mugnoli, A. (1985). *J. Appl. Cryst.* **18**, 183-184.

Mugnoli, A. (1990). *CAVITY.* Program to locate and measure spherical voids in a crystal structure. Univ. of Genoa, Italy.

Nardelli, M. (1983a). *Comput. Chem.* **7**, 95-98.

Nardelli, M. (1983b). *Acta Cryst.* C**39**, 1141-1142.

Nardelli, M. & Mangia, A. (1984). *Ann. Chim. (Rome)*, **74**, 163-174.

Sheldrick, G. M. (1976). *SHELX76.* Program for crystal structure determination. Univ. of Cambridge, England.

Spek, A. L. (1988). *J. Appl. Cryst.* **21**, 578-579.

Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139-1144.

Structure of a Novel Carbapenem Antibiotic, Meropenem

KAZUNORI YANAGI

Tsukuba Research Laboratory, Sumitomo Chemical Co. Ltd, 6 Kitahara, Tsukuba, Ibaraki 300-32, Japan

YUTAKA TAKEUCHI AND MAKOTO SUNAGAWA

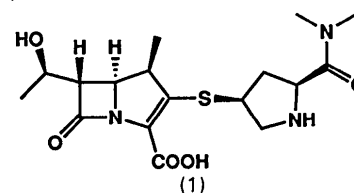*Research Laboratories, Sumitomo Pharmaceuticals Co. Ltd, 3-1-98 Konohana-ku, Osaka 554, Japan*

Abstract

The absolute configuration of the title compound, (4R,5S,6S)-3-[(3S,5S)-5-dimethylaminocarbonylpyrrolidin-3-ylthio]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate, is confirmed. Meropenem crystallized as a zwitterion with the three molecules of water. The sum of the three bond angles about the N atom of the β-lactam ring is 329.1° and the deviation of the N atom from the plane defined by the three adjacent atoms is 0.457 Å. Short intramolecular contacts are observed between the 1β-methyl group and the β-lactam ring.

Comment

Thienamycin and the related naturally occurring compounds are β-lactam antibiotics possessing potent antibacterial activity (Albers-Schönberg *et al.*, 1978). They are also chemically unstable and easily metabolized by renal dehydropeptidase-I (DHP-I). Meropenem (1) is a new 1β-methylcarbapenem antibiotic possessing excellent antibacterial activity and chemical stability with high stability to DHP-I (Sunagawa, Matsumura, Inoue, Fukasawa & Kato, 1990).
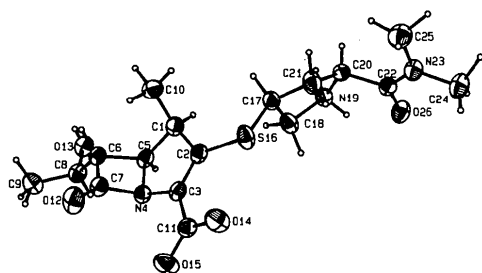

(1)

Fig. 1. View of meropenem showing the labelling of the non-H atoms. Thermal ellipsoids are shown at 50% probability levels. H atoms are drawn as small circles of arbitrary radius.

Meropenem crystallized as a zwitterion with a negative charge on the carboxyl group and a positive charge on the pyrrolidine ring N atom. The H atom H(N19A) of the pyrrolidine ring is separated by 2.00(9) Å from the O atom of the dimethylaminocarbonyl group, suggesting that there is an intramolecular hydrogen bond. The conformation of the dimethylaminocarbonyl group is fixed by the formation of an intramolecular hydrogen bond. Intermolecular hydrogen bonds are also found between the N atom of the pyrrolidine ring, the carboxyl group and the three water molecules.

The sum of the three bond angles around the β-lactam N atom (ΣN) is 329.1° and the distance of that N atom from the plane of its three attached C atoms (D) is 0.457 Å. These values are similar to those of the thienamycin derivative (Albers-Schönberg *et al.*, 1978) which has $\Sigma N = 325.9°$ and $D = 0.49$ Å. Cohen (1983) evaluated the significance parameter for antibacterial activity by measuring the distance between the β-lactam O atom and the carboxylate C atom; distances between 3.0 and 3.9 Å were observed in active compounds. In the case of meropenem, the distance is 3.617(3) Å.

The 1β-methyl group C(10) makes a short contact with the β-lactam ring. The steric effect of 1β-methyl substitution may contribute to the enhanced chemical and metabolic stability of the meropenem.

Experimental

Crystal data

$C_{17}H_{25}N_3O_5S.3H_2O$
$M_r = 437.52$
Monoclinic
$P2_1$
$a = 9.279\ (1)$ Å
$b = 14.035\ (1)$ Å
$c = 9.123\ (1)$ Å
$\beta = 117.37\ (1)°$
$V = 1055.1$ Å^3
$Z = 2$
$D_x = 1.377$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 21-29°$
$\mu = 1.75$ mm^{-1}
$T = 295$ K
Prism
$0.45 \times 0.25 \times 0.05$ mm
Colorless

Data collection

Enraf-Nonius CAD-4 diffractometer
$R_{int} = 0$
$\theta_{max} = 69.88°$

$\omega/2\theta$ scans
Absorption correction: none
2086 measured reflections
2086 independent reflections
1994 observed reflections
[$I > 3.0\sigma(I)$]

$h = -11 \rightarrow 11$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 11$
3 standard reflections frequency: 60 min intensity variation: none

Refinement

Refinement on F
Final $R = 0.034$
$wR = 0.046$
$S = 1.820$
1994 reflections
386 parameters
All H-atom parameters refined
$w = 4I/[\sigma^2(I) + 0.0025I^2]$

$(\Delta/\sigma)_{max} = 0.044$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B)

Data collection: Enraf-Nonius CAD-4 software. Cell refinement: Enraf-Nonius CAD-4 software. Data reduction: *BEGIN* (Enraf-Nonius, 1985). Program(s) used to solve structure: *MITHRIL* (Gilmore, 1984). Program(s) used to refine structure: *LSFM* (Enraf-Nonius, 1985). Molecular graphics: *ORTEP* (Johnson, 1976). Software used to prepare material for publication: *ESD, PTABLE* and *BTABLE* (Enraf-Nonius, 1985).

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$$U_{eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
S(16)	0.55458 (6)	0.5	0.74195 (6)	0.0399 (1)
O(12)	0.3509 (2)	0.7147 (2)	0.1656 (3)	0.0512 (6)
O(13)	0.9029 (2)	0.7615 (1)	0.3140 (2)	0.0388 (4)
O(14)	0.2714 (2)	0.4566 (2)	0.4370 (2)	0.0474 (5)
O(15)	0.2596 (2)	0.4789 (2)	0.1919 (2)	0.0527 (5)
O(26)	0.9236 (2)	0.2349 (2)	1.2017 (2)	0.0410 (4)
N(4)	0.5389 (2)	0.5967 (1)	0.3284 (2)	0.0293 (4)
N(19)	0.9733 (2)	0.3862 (2)	1.0718 (2)	0.0330 (5)
N(23)	0.7839 (2)	0.2972 (2)	1.3249 (2)	0.0348 (5)
C(1)	0.7161 (2)	0.6279 (2)	0.6129 (3)	0.0319 (5)
C(2)	0.5845 (2)	0.5536 (2)	0.5860 (3)	0.0299 (5)
C(3)	0.4799 (2)	0.5444 (2)	0.4245 (2)	0.0291 (5)
C(5)	0.7049 (2)	0.6340 (2)	0.4393 (3)	0.0294 (5)
C(6)	0.6578 (2)	0.7263 (2)	0.3333 (2)	0.0299 (5)
C(7)	0.4858 (2)	0.6852 (2)	0.2538 (3)	0.0324 (5)
C(8)	0.7379 (2)	0.7365 (2)	0.2200 (3)	0.0333 (5)
C(9)	0.6481 (3)	0.8061 (2)	0.0798 (3)	0.0450 (7)
C(10)	0.6765 (3)	0.7205 (2)	0.6755 (3)	0.0418 (6)
C(11)	0.3240 (2)	0.4899 (2)	0.3453 (3)	0.0320 (5)
C(17)	0.7558 (3)	0.4936 (2)	0.9184 (2)	0.0344 (5)
C(18)	0.8655 (3)	0.4192 (2)	0.8991 (3)	0.0385 (6)
C(20)	0.8868 (3)	0.4029 (2)	1.1749 (2)	0.0302 (5)
C(21)	0.7285 (3)	0.4534 (2)	1.0595 (3)	0.0401 (6)
C(22)	0.8653 (2)	0.3047 (2)	1.2365 (2)	0.0297 (5)
C(24)	0.7619 (3)	0.2022 (2)	1.3767 (3)	0.0448 (6)
C(25)	0.7156 (3)	0.3767 (2)	1.3742 (3)	0.0481 (7)
O(W1)	0.0866 (2)	0.4499 (2)	0.5999 (2)	0.0521 (6)
O(W2)	0.9964 (2)	0.1960 (2)	0.9142 (2)	0.0624 (7)
O(W3)	0.1787 (4)	0.5468 (2)	-0.1173 (3)	0.0848 (9)

Table 2. *Geometric parameters* (Å, °)

S(16)—C(2)	1.741 (3)	C(1)—C(2)	1.537 (3)
O(12)—C(7)	1.208 (3)	C(1)—C(5)	1.542 (4)
O(13)—C(8)	1.412 (3)	C(1)—C(10)	1.531 (4)
O(14)—C(11)	1.237 (3)	C(2)—C(3)	1.347 (3)
O(15)—C(11)	1.253 (3)	C(3)—C(11)	1.496 (3)
O(26)—C(22)	1.229 (3)	C(5)—C(6)	1.554 (3)

N(4)—C(3)	1.432 (3)	C(6)—C(7)	1.530 (3)
N(4)—C(5)	1.495 (2)	C(6)—C(8)	1.532 (4)
N(4)—C(7)	1.393 (3)	C(8)—C(9)	1.517 (3)
N(19)—C(18)	1.500 (3)	C(17)—C(18)	1.523 (4)
N(19)—C(20)	1.508 (4)	C(17)—C(21)	1.530 (4)
N(23)—C(22)	1.339 (4)	C(20)—C(21)	1.532 (3)
N(23)—C(24)	1.461 (4)	C(20)—C(22)	1.535 (3)
N(23)—C(25)	1.453 (4)		
N(19)—O(26)	2.574 (3)	O(W1)—O(W3^{iii})	2.685 (3)
N(19)—O(15^i)	2.697 (3)	O(W2)—O(12^{iv})	2.971 (3)
O(13)—O(W1^{ii})	2.748 (3)	O(W2)—O(13^v)	2.801 (3)
O(W1)—O(14)	2.739 (3)	O(W3)—O(26^{ii})	2.791 (3)
O(15)—O(W3)	2.735 (3)		
C(3)—N(4)—C(5)	109.3 (2)	C(5)—C(6)—C(8)	114.4 (2)
C(3)—N(4)—C(7)	127.4 (2)	C(7)—C(6)—C(8)	116.1 (2)
C(5)—N(4)—C(7)	92.4 (2)	O(12)—C(7)—N(4)	131.0 (2)
C(18)—N(19)—C(20)	108.5 (2)	O(12)—C(7)—C(6)	136.3 (2)
C(22)—N(23)—C(24)	117.9 (2)	N(4)—C(7)—C(6)	92.7 (2)
C(22)—N(23)—C(25)	125.0 (2)	O(13)—C(8)—C(6)	109.9 (2)
C(24)—N(23)—C(25)	117.1 (2)	O(13)—C(8)—C(9)	112.0 (2)
C(2)—C(1)—C(5)	101.6 (2)	C(6)—C(8)—C(9)	112.3 (2)
C(2)—C(1)—C(10)	109.1 (2)	O(14)—C(11)—O(15)	125.1 (2)
C(5)—C(1)—C(10)	114.9 (2)	O(14)—C(11)—C(3)	117.4 (2)
S(16)—C(2)—C(1)	125.1 (1)	O(15)—C(11)—C(3)	117.4 (2)
S(16)—C(2)—C(3)	123.2 (2)	C(18)—C(17)—C(21)	102.8 (2)
C(1)—C(2)—C(3)	111.1 (2)	N(19)—C(18)—C(17)	104.4 (2)
N(4)—C(3)—C(2)	109.5 (2)	N(19)—C(20)—C(21)	105.1 (2)
N(4)—C(3)—C(11)	121.6 (2)	N(19)—C(20)—C(22)	106.5 (2)
C(2)—C(3)—C(11)	128.9 (2)	C(21)—C(20)—C(22)	114.9 (2)
N(4)—C(5)—C(1)	103.8 (2)	C(17)—C(21)—C(20)	105.7 (2)
N(4)—C(5)—C(6)	87.9 (1)	O(26)—C(22)—N(23)	122.0 (2)
C(1)—C(5)—C(6)	123.6 (2)	O(26)—C(22)—C(20)	118.3 (2)
C(5)—C(6)—C(7)	85.1 (2)	N(23)—C(22)—C(20)	119.7 (2)

Symmetry codes: (i) $1 + x, y, 1 + z$; (ii) $1 - x, \frac{1}{2} + y, 1 - z$; (iii) $x, y, 1 + z$; (iv) $1 - x, y - \frac{1}{2}, 1 - z$; (v) $2 - x, y - \frac{1}{2}, 1 - z$.

The ω-scan width was $(1.0 + 0.15\tan\theta)°$. Refinement was by full- matrix least-squares methods. Refinement of the other enantiomer under identical conditions yielded $R = 0.038$, $wR = 0.053$ and $S = 2.077$. The better fit for the atomic coordinates presented in Table 1 is in agreement with the known absolute configuration. Calculations were performed on a MicroVAX II computer.

References

Albers-Schönberg, G., Arison, B. H., Hensens, O. D., Hirshfield, J., Hoogsteen, K., Kaczka, E. A., Rhodes, R. E., Kahan, J. S., Kahan, F. M., Ratcliffe, R. W., Walton, E., Ruswinkle, L. J., Morin, R. B. & Christensen, B. G. (1978). *J. Am. Chem. Soc.* **100**, 6491-6499.
Cohen, N. C. (1983). *J. Med. Chem.* **26**, 259-264.
Enraf-Nonius (1985). *Structure Determination Package.* Enraf-Nonius, Delft, The Netherlands.
Gilmore, C. J. (1984). *J. Appl. Cryst.* **17**, 42-46.
Johnson, C. K. (1976). *ORTEPII.* Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Sunagawa, M., Matsumura, H., Inoue, T., Fukasawa, M. & Kato, M. (1990). *J. Antibiot.* **43**, 519-532.