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Structure of a 7α-Methoxy-1-oxacephem: Diphenylmethyl 7α-Methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthio)methyl-7β-phenylacetamido-1-oxa-1-dethia-3-cephem-4-carboxylate*

BY MOTOO SHIRO, HIROSHI NAKAI, HIROSHI ONOUE AND MASAYUKI NARISADA

Shionogi Research Laboratories, Shionogi & Co. Ltd, Fukushima-ku, Osaka 553, *Japan*

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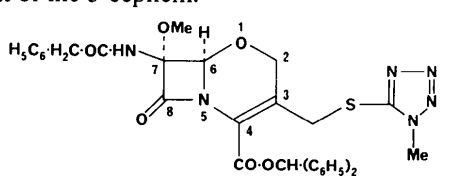
Abstract. $C_{32}H_{30}N_6O_6S$, orthorhombic, $P2_12_12_1$, a = 14·010 (2), b = 23·170 (2), c = 9·645 (2) Å, Z = 4, D_x = 1·329 Mg m^{-3}. The structure was solved by the direct method and refined by the block-diagonal least-squares technique to R = 0·040 for 2970 reflexions. The N–C and C=O bond lengths in the β-lactam amide group are 1·393 (4) and 1·201 (4) Å, respectively. The N atom is displaced by 0·220 (2) Å from the plane of the three attached C atoms.

Introduction. 1-Oxacephems are synthetic cephalosporin analogues possessing the 1-oxa-1-dethia-3-cephem skeleton (abbreviated hereafter as 1-oxacephem skeleton), some of which exhibit antibacterial activity several times as potent as that of the corresponding cephalosporins (Narisada, Onoue & Nagata, 1977; Narisada *et al.*, 1979). For cephalosporins, the correlations between the biological activity and the geometrical features of the 3-cephem have been elucidated by Sweet (1972). Therefore, it is of interest to compare the structure of the 1-oxacephem skeleton with that of the 3-cephem.



Crystals of the title compound, the diphenylmethyl ester of one of the active 7α-methoxy-1-oxacephems, were obtained from a dichloromethane–ethanol solution. The systematic absences are $h00$ h odd, $0k0$ k odd, and $00l$ l odd. Three-dimensional intensity data were collected on a Rigaku diffractometer with graphite-monochromatized Cu $K\alpha$ radiation and a crystal of dimensions 0·3 × 0·2 × 0·2 mm. Integrated intensities were measured in the range $\theta \leq 70°$ with an ω–2θ scan, a constant scan speed of 0·05° s^{-1} and an ω scan range of (1·0 + 0·2 tan θ)°. The 3264 independent intensities were corrected for Lorentz and polarization factors, but not for absorption effects.

The structure was solved by use of the program *MULTAN* 76 (Main, Lessinger, Woolfson, Germain & Declercq, 1976). In a difference electron density map calculated after block-diagonal least-squares refinement, all the H atoms were located. Successive refinement of the positional and anisotropic thermal parameters of the non-hydrogen atoms gave an R value ($\sum|\Delta F|/\sum|F_o|$) of 0·040 for 2970 reflexions. The atomic scattering factors were calculated using the analytical expression $f = \sum[a_i \exp(-b_i\lambda^{-2}\sin^2\theta)] + c$ ($i = 1 \sim 4$) (*International Tables for X-ray Crystallography*, 1974). The weighting scheme used was $w = 1/\sigma^2(F_o)$ for $|F_c| \geq \sigma(F_o)$ and $w = 0$ for $|F_c| < \sigma(F_o)$ or $|\Delta F| \geq 3\sigma(F_o)$. $\sigma(F_o)$ was estimated as $\sigma(F_o) = [\sigma_1^2(F_o) + 0{\cdot}00119|F_o|^2]^{1/2}$, where $\sigma_1(F_o)$ is the standard deviation due to counting errors (Grant, Killean & Lawrence, 1969).†

† Lists of thermal parameters of the non-hydrogen atoms, positional parameters of the H atoms, and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35513 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

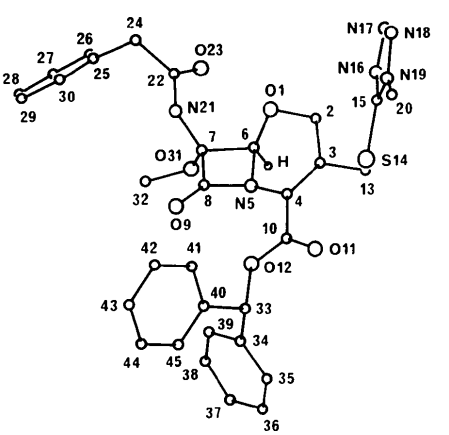


Fig. 1. Perspective view of the molecule with the atom-numbering scheme.

* Diphenylmethyl 7α-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthio)-methyl-6-oxo-7β-phenylacetamide-6,7-dihydro-2*H*,7a*H*-azeto-[2,1-*b*]-*m*-oxazine-4-carboxylate.

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Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors* ($\times 10^3$ Å^2) *with e.s.d.'s in parentheses*

	x	y	z	U_{eq}		x	y	z	U_{eq}
O(1)	−230 (1)	214 (1)	−2889 (2)	36 (1)	C(24)	−3459 (2)	279 (1)	−2526 (4)	46 (1)
C(2)	764 (2)	370 (1)	−2926 (3)	39 (1)	C(25)	−4203 (2)	−199 (1)	−2590 (4)	47 (1)
C(3)	1394 (2)	−8 (1)	−2029 (3)	35 (1)	C(26)	−4558 (3)	−375 (2)	−3879 (4)	69 (1)
C(4)	1071 (2)	−501 (1)	−1493 (3)	31 (1)	C(27)	−5184 (4)	−840 (2)	−3976 (5)	94 (2)
N(5)	159 (2)	−686 (1)	−1953 (2)	34 (1)	C(28)	−5470 (3)	−1120 (2)	−2775 (6)	90 (2)
C(6)	−312 (2)	−381 (1)	−3091 (3)	33 (1)	C(29)	−5125 (3)	−952 (2)	−1509 (5)	82 (2)
C(7)	−1267 (2)	−652 (1)	−2619 (3)	33 (1)	C(30)	−4487 (3)	−490 (2)	−1423 (4)	60 (1)
C(8)	−688 (2)	−888 (1)	−1373 (3)	35 (1)	O(31)	−1537 (2)	−1066 (1)	−3593 (2)	45 (1)
O(9)	−879 (2)	−1140 (1)	−321 (3)	54 (1)	C(32)	−2295 (3)	−1441 (1)	−3150 (5)	70 (1)
C(10)	1607 (2)	−896 (1)	−558 (3)	36 (1)	C(33)	1531 (2)	−1832 (1)	544 (3)	44 (1)
O(11)	2378 (2)	−779 (1)	−70 (3)	52 (1)	C(34)	1512 (3)	−2374 (1)	−328 (3)	52 (1)
O(12)	1126 (1)	−1379 (1)	−345 (2)	44 (1)	C(35)	2329 (4)	−2700 (2)	−497 (5)	87 (2)
C(13)	2408 (2)	206 (1)	−1899 (3)	39 (1)	C(36)	2298 (5)	−3204 (2)	−1351 (7)	119 (2)
S(14)	2673 (1)	573 (1)	−264 (1)	45 (1)	C(37)	1435 (6)	−3372 (2)	−1949 (6)	118 (2)
C(15)	2342 (2)	1277 (1)	−660 (3)	41 (1)	C(38)	648 (5)	−3042 (2)	−1801 (6)	96 (2)
N(16)	1859 (2)	1463 (1)	−1743 (3)	50 (1)	C(39)	661 (3)	−2549 (2)	−968 (5)	68 (1)
N(17)	1755 (2)	2045 (1)	−1548 (4)	61 (1)	C(40)	930 (2)	−1868 (1)	1854 (3)	43 (1)
N(18)	2154 (3)	2202 (1)	−389 (4)	66 (1)	C(41)	493 (3)	−1392 (2)	2414 (4)	59 (1)
N(19)	2541 (2)	1722 (1)	166 (3)	54 (1)	C(42)	−32 (3)	−1435 (2)	3636 (4)	69 (1)
C(20)	3050 (4)	1740 (2)	1481 (4)	74 (1)	C(43)	−103 (3)	−1961 (2)	4323 (5)	76 (1)
N(21)	−2019 (2)	−280 (1)	−2166 (2)	35 (1)	C(44)	352 (5)	−2432 (2)	3790 (5)	93 (2)
C(22)	−2539 (2)	35 (1)	−3096 (3)	37 (1)	C(45)	857 (3)	−2391 (2)	2547 (4)	69 (1)
O(23)	−2296 (2)	89 (1)	−4305 (2)	50 (1)					

Table 2. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

O(1)–C(2)	1·439 (4)	N(21)–C(22)	1·367 (4)
O(1)–C(6)	1·397 (3)	C(22)–O(23)	1·221 (4)
C(2)–C(3)	1·515 (4)	C(22)–C(24)	1·511 (4)
C(3)–C(4)	1·333 (4)	C(24)–C(25)	1·522 (5)
C(3)–C(13)	1·510 (4)	C(25)–C(26)	1·400 (5)
C(4)–N(5)	1·419 (3)	C(25)–C(30)	1·371 (5)
C(4)–C(10)	1·488 (4)	C(26)–C(27)	1·392 (7)
N(5)–C(6)	1·463 (3)	C(27)–C(28)	1·387 (8)
N(5)–C(8)	1·393 (4)	C(28)–C(29)	1·370 (8)
C(6)–C(7)	1·546 (4)	C(29)–C(30)	1·397 (7)
C(7)–C(8)	1·550 (4)	O(31)–C(32)	1·437 (6)
C(7)–N(21)	1·430 (3)	C(33)–C(34)	1·512 (5)
C(7)–O(31)	1·395 (4)	C(33)–C(40)	1·521 (4)
C(8)–O(9)	1·201 (4)	C(34)–C(35)	1·381 (6)
C(10)–O(11)	1·209 (4)	C(34)–C(39)	1·402 (6)
C(10)–O(12)	1·322 (4)	C(35)–C(36)	1·430 (9)
O(12)–C(33)	1·469 (4)	C(36)–C(37)	1·395 (11)
C(13)–S(14)	1·830 (3)	C(37)–C(38)	1·349 (11)
S(14)–C(15)	1·738 (3)	C(38)–C(39)	1·397 (8)
C(15)–N(16)	1·317 (4)	C(40)–C(41)	1·372 (5)
C(15)–N(19)	1·332 (4)	C(40)–C(45)	1·388 (6)
N(16)–N(17)	1·369 (5)	C(41)–C(42)	1·393 (6)
N(17)–N(18)	1·302 (5)	C(42)–C(43)	1·391 (6)
N(18)–N(19)	1·348 (5)	C(43)–C(44)	1·364 (8)
N(19)–C(20)	1·456 (6)	C(44)–C(45)	1·395 (8)

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

C(2)–O(1)–C(6)	108·9 (2)	C(15)–N(19)–C(20)	130·2 (3)
O(1)–C(2)–C(3)	113·9 (2)	N(18)–N(19)–C(20)	121·3 (3)
C(2)–C(3)–C(4)	121·3 (3)	C(7)–N(21)–C(22)	120·9 (2)
C(2)–C(3)–C(13)	113·9 (2)	N(21)–C(22)–O(23)	122·2 (3)
C(4)–C(3)–C(13)	124·7 (3)	N(21)–C(22)–C(24)	114·6 (2)
C(3)–C(4)–N(5)	116·3 (2)	O(23)–C(22)–C(24)	123·2 (3)
C(3)–C(4)–C(10)	126·2 (2)	C(22)–C(24)–C(25)	107·3 (3)
N(5)–C(4)–N(10)	117·3 (2)	C(24)–C(25)–C(26)	119·4 (3)
C(4)–N(5)–C(6)	119·7 (2)	C(24)–C(25)–C(30)	121·6 (3)
C(4)–N(5)–C(8)	138·0 (2)	C(26)–C(25)–C(30)	118·9 (3)
C(6)–N(5)–C(8)	94·6 (2)	C(25)–C(26)–C(27)	120·6 (4)
O(1)–C(6)–N(5)	109·6 (2)	C(26)–C(27)–C(28)	119·2 (5)
O(1)–C(6)–C(7)	115·5 (2)	C(27)–C(28)–C(29)	120·6 (5)
N(5)–C(6)–C(7)	88·5 (2)	C(28)–C(29)–C(30)	119·8 (5)
C(6)–C(7)–C(8)	85·3 (2)	C(25)–C(30)–C(29)	120·9 (4)
C(6)–C(7)–N(21)	118·9 (2)	C(7)–O(31)–C(32)	114·6 (3)
C(6)–C(7)–O(31)	108·4 (2)	O(12)–C(33)–C(34)	105·2 (3)
C(8)–C(7)–N(21)	111·2 (2)	O(12)–C(33)–C(40)	108·1 (2)
C(8)–C(7)–O(31)	114·9 (2)	C(34)–C(33)–C(40)	114·0 (3)
N(21)–C(7)–O(31)	114·9 (2)	C(33)–C(34)–C(35)	120·4 (4)
N(5)–C(8)–C(7)	90·9 (2)	C(33)–C(34)–C(39)	120·0 (3)
N(5)–C(8)–O(9)	133·8 (3)	C(35)–C(34)–C(39)	119·6 (4)
C(7)–C(8)–O(9)	135·3 (3)	C(34)–C(35)–C(36)	119·3 (5)
C(4)–C(10)–O(11)	123·3 (3)	C(35)–C(36)–C(37)	119·5 (6)
C(4)–C(10)–O(12)	110·9 (2)	C(36)–C(37)–C(38)	120·4 (7)
O(11)–C(10)–O(12)	125·8 (3)	C(37)–C(38)–C(39)	120·9 (6)
C(10)–O(12)–C(33)	119·9 (2)	C(34)–C(39)–C(38)	120·0 (4)
C(3)–C(13)–S(14)	114·5 (2)	C(33)–C(40)–C(41)	122·0 (3)
C(13)–S(14)–C(15)	101·1 (1)	C(33)–C(40)–C(45)	119·3 (3)
S(14)–C(15)–N(16)	128·2 (2)	C(41)–C(40)–C(45)	118·6 (3)
S(14)–C(15)–N(19)	122·6 (2)	C(40)–C(41)–C(42)	120·7 (4)
N(16)–C(15)–N(19)	109·2 (3)	C(41)–C(42)–C(43)	120·2 (4)
C(15)–N(16)–N(17)	105·5 (3)	C(42)–C(43)–C(44)	119·2 (5)
N(16)–N(17)–N(18)	110·3 (3)	C(43)–C(44)–C(45)	120·4 (5)
N(17)–N(18)–N(19)	106·4 (3)	C(40)–C(45)–C(44)	120·7 (4)
C(15)–N(19)–N(18)	108·5 (3)		

Discussion. Final positional and isotropic thermal parameters are listed in Table 1. Bond distances and angles are given in Tables 2 and 3, respectively. A perspective view of the molecule is shown in Fig. 1.

In the crystal, the molecules related by a 2_1 axis in the **c** direction are linked by hydrogen bonds, $\rangle NH\cdots O{=}C\langle$, between the exocyclic amide groups.

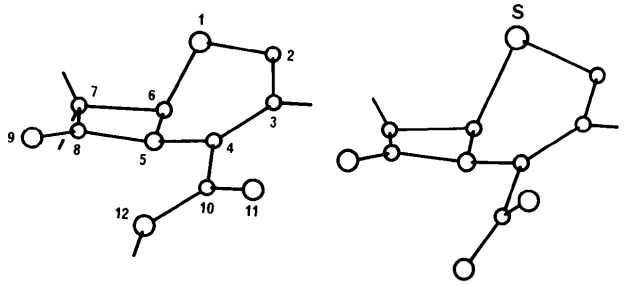

Fig. 2. Comparison of the 1-oxacephem (left) and the 3-cephem (right) skeletons.

Fig. 2 gives a comparison of the geometries of the 1-oxacephem skeleton (I) and the 3-cephem skeleton (II) of cephapyrine (Declercq, Germain, Moreaux & Van Meerssche, 1977) which is very similar to that of cephaloridine (Sweet & Dahl, 1970). The bond angles C(2)–O(1)–C(6), N(5)–C(4)–C(10), C(4)–N(5)–C(6) and C(4)–N(5)–C(8) in (I) are significantly different from the corresponding angles in (II) [93·2 (5), 110·5 (8), 125·4 (8) and 132·4 (8)°, respectively]. The twist angle of the carboxyl group out of the C(3)–C(4)–N(5) plane is 6·0 (4)° for (I) and 35·3 (7)° for (II).

The N(5) atom in this molecule adopts a non-planar conformation; its displacement from the plane of C(4), C(6) and C(8) is 0·220 (2) Å. The C(4)–N(5) bond [1·419 (3) Å] is comparable with those of cephaloridine and cephapyrine [1·39 (1) and 1·415 (11) Å, respectively] in which an enamine resonance, $>N-C=C< \leftrightarrow >\overset{+}{N}=C-\overset{-}{C}<$, occurs. This indicates that the lone-pair of electrons of the N atom in this compound is partly delocalized into the π-orbital system of the $>C(3)=C(4)-C(10)O(11)-O(12)-$ moiety which is almost planar.

The bond lengths of 1·393 (4) and 1·201 (4) Å in the β-lactam amide group [N(5)–C(8), C(8)–O(9)] differ from those of 1·367 (4) and 1·221 (4) Å in the exocyclic amide group [N(21)–C(22), C(22)=O(23)], indicating a reduction of normal amide resonance, $O=C-N< \leftrightarrow \bar{O}-C=\overset{+}{N}<$, in the β-lactam ring.

For penicillins and cephalosporins, the biological activity is correlated with the lability of the β-lactam amide bond to base hydrolysis, and this amide bond is more easily hydrolyzed as the contribution of normal amide resonance to the bond decreases (Sweet, 1972). Also, the non-planarity of the β-lactam N atom and, especially in the case of cephalosporins, the enamine resonance reduce the amide resonance. With a decrease in the amide resonance, the C–N bond is lengthened [1·37 (1) Å for penicillins, 1·38 (1) Å for cephalosporins] while the C=O bond is shortened [1·20 (1), 1·21 (1) Å, respectively]. Thus, the stereochemical characteristics exhibited by the 1-oxacephem are common to those of cephalosporins.

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