Crystal and Molecular Structure of 4-Acetyl-3-methyl-7β-phenoxyacetamido-Δ^3-cephem

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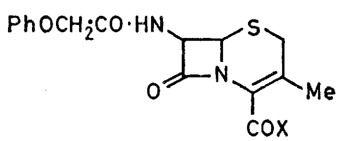
The crystal structure of the title compound (4) has been determined by three-dimensional diffraction methods. Crystals are orthorhombic, space group $P2_12_12_1$ with $Z = 4$, unit cell dimensions $a = 23.771(7)$, $b = 8.833(2)$, $c = 7.943(7)$ Å. The structure has been solved by direct methods and refined by least-squares to R 0.051. The relevant molecular parameters are compared with those of other Δ^3-cephem derivatives. In particular the same distortions of the β-lactam ring are observed; the lactam-nitrogen atom is out of the plane of its bonded carbon atoms by 0.20 Å.

In recent years the chemistry of cephalosporin antibiotics has received tremendous interest. Although several attempts have been made to rationalize the structure–activity relationship of these β-lactam antibiotics,[1] it is not possible to foresee at present the *a priori* biological activity of new semisynthetic cephalosporins. For this reason considerable effort has been made in synthesizing new cephalosporin derivatives by both changing substituents linked to the Δ^3-cephem skeleton present in the naturally occurring cephalosporins and by attempting to modify the Δ^3-cephem skeleton itself.[1,2]

As a continuation of our studies [3] on the chemistry of the dihydrothiazine ring moiety of cephalosporins, the molecular structure of 3-methyl-4-acetyl-7β-phenoxyacetamido-Δ^3-cephem (4) appeared particularly interesting in order both to contribute to a better knowledge of



X
(1) OH
(2) Cl
(3) CHN2
(4) Me

the relationship between structure and biological activity of Δ^3-cephem derivatives, and to rationalize the stereochemical results of some reactions of the ketone (4) itself. There has been little information concerning the molecular structures of Δ^3-cephem derivatives carrying substituents on C(4) other than a carboxylic group or its salts or esters.

Ketone (4) was prepared by reaction of the acid chloride (2) with diazomethane, followed by treatment of the diazoketone (3) with 47% hydroiodic acid. The acid chloride (2) was obtained from the acid (1) by reaction with oxalyl chloride in CH_2Cl_2 in the presence of small amounts of dimethylformamide (DMF). Compound (4) was tested *in vitro* against several strains of gram-positive and gram-negative bacteria, exhibiting minimal inhibitory concentrations >100 μg ml^{-1} against any bacteria tested.

We here report the crystal structure of (4).

EXPERIMENTAL

^{1}H N.m.r. spectra were performed on a JEOL PS 100 spectrometer in $CDCl_3$ solutions using tetramethylsilane as internal standard. I.r. spectra were taken for Nujol mulls on a Perkin-Elmer Infracord 137.

Preparation of Compound (4).—*3-Methyl-7β-phenoxyacetamido-Δ^3-cephem-4-carbonyl chloride* (2).[4] A solution of oxalyl chloride (8.9 g, 0.070 mol) in anhydrous CH_2Cl_2 (15 ml) was added, slowly and with stirring, to an ice-cold suspension of 3-methyl-7β-phenoxyacetamido-Δ^3-cephem-4-carboxylic acid (1) [5] (10.0 g, 0.029 mol) in a mixture of anhydrous CH_2Cl_2 (160 ml) and DMF (0.5 ml). The reaction mixture was stirred at 0 °C for 1 h, and solvent was then evaporated under reduced pressure at <10 °C. Crystallization of the crude residue from CH_2Cl_2–hexane yielded pure (2) (8.0 g, 76%) as a yellow solid (Found: C, 52.50; H, 4.35; N, 7.50. Calc. for $C_{16}H_{15}ClN_2O_4S$: C, 52.38; H, 4.12; N, 7.63%); $\nu_{max.}$ 1 772 (β-lactam), 1 733 (acid chloride), and 1 690 cm^{-1} (amide); δ 2.19 (3 H, s, CH_3), 3.40 (2 H, s, SCH_2), 5,11 (1 H, d, J 4.5 Hz, CHS), and 5.88 (1 H, q, J 4.5 and 9.0 Hz, NCH).

4-Diazoacetyl-3-methyl-7β-phenoxyacetamido-Δ^3-cephem (3). A 0.4M-ethereal solution of CH_2N_2 (150 ml) was added in portions during 20 min at -15 °C to a stirred solution of acid chloride (2) (7.0 g, 0.019 mol) in CH_2Cl_2 (100 ml). The reaction mixture was stirred at -15 °C for an additional 1 h and then evaporated under reduced pressure. Recrystallization of the solid residue from acetone–hexane gave pure (3) (4.2 g, 59%), m.p. 144—146 °C (decomp.) (Found: C, 54.60; H, 4.50; N, 14.85. Calc. for $C_{17}H_{16}N_4O_4S$: C, 54.82; H, 4.33; N, 15.04%); $\nu_{max.}$ 2 140 (diazo), 1 770 (β-lactam), and 1 673 cm^{-1} (amide); δ 2.14 (3 H, s, CH_3), 3.16 and 3.45 (2 H, 2 d, J 17.4 Hz, SCH_2), 5.04 (1 H, d,

[1] (*a*) E. H. Flynn, 'Cephalosporins and Penicillins. Chemistry and Biology,' Academic Press, New York, 1972; (*b*) J. Cs. Jászberényi and T. E. Gunda, *Progr. Medicin. Chem.*, 1975, **12**, 395; (*c*) R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.

[2] P. G. Sammes, *Chem. Rev.*, 1976, **76**, 113.

[3] A. Balsamo, P. Crotti, B. Macchia, F. Macchia, G. Nannini, E. Dradi, and A. Forgione, *J. Org. Chem.*, 1976, **41**, 2150.

[4] C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, 1970, **35**, 2429.

[5] R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, **36**, 1259.

J 4.5 Hz, CHS), 5.70 (1 H, s, CHN_2), and 5.79 (1 H, q, J 4.5 and 9.0 Hz, NCH).

4-Acetyl-3-methyl-7β-phenoxyacetamido-Δ^3-cephem (4). A solution of (3) (4.4 g, 0.012 mol) in $CHCl_3$ (600 ml) was shaken with 47% HI (20 ml) for 10 min. The reaction mixture was then washed (aqueous 0.1N-$Na_2S_2O_3$ and H_2O) and the filtered organic phase then evaporated *in vacuo*. Recrystallization of the solid residue from acetone–hexane afforded pure (4) (2.4 g, 58%), m.p. 156—157 °C (Found: C, 58.75; H, 5.35; N, 7.90. $C_{17}H_{18}N_2O_4S$ requires C, 58.94; H, 5.24; N, 8.09%); $\nu_{max.}$ 1 760 (β-lactam), 1 690 (ketone), and 1 665 cm^{-1} (amide); δ 2.10 (3 H, s, CH_3), 2.42 (3 H, s, $COCH_3$), 3.21 and 3.54 (2 H, 2 d, J 18.6 Hz, SCH_2), 5.13 (1 H, d, J 4.5 Hz, CHS), and 5.94 (1 H, q, J 4.5 and 9.7 Hz, NCH); m/e 346 (M^+).

Crystals of (4) suitable for X-ray analysis, m.p. 150—151 °C, were obtained by slow evaporation of a dichloromethane solution containing di-isopropyl ether.

Antibacterial Activity.—The activity of (4) was tested against 36 strains of gram-positive and gram-negative bacteria. A solution of the compound in dimethyl sulphoxide was incorporated at several concentrations in brain heart infusion agar to which 10% horse serum had been added; the agar surface was inoculated with an overnight culture of the bacterial strains, diluted 1 : 25. Readings of the minimal inhibitory concentrations (MIC) were made after 24 h at 37 °C.

X-*Ray Data and Structure Determination*.—Preliminary oscillation and Weissenberg photographs established the orthorhombic space group $P2_12_12_1$ and gave starting cell parameters which were successively refined by a least-squares fit to the 2θ, ω, and χ values for a number of carefully-centred reflections on a Siemens A.E.D. computer-controlled diffractometer; Ni-filtered Cu-K_α radiation (λ = 1.541 8 Å) was used.

Crystal data. $C_{17}H_{18}N_2O_4S$, M = 346.4. Orthorhombic, a = 23.771(7), b = 8.333(2), c = 7.943(7) Å, U = 1668(2) $Å^3$, Z = 4, D_c = 1.380 g cm^{-3}, $F(000)$ = 728. Space group $P2_12_12_1$. Cu-K_α radiation λ = 1.541 8 Å; μ(Cu-K_α) = 18.9 cm^{-1}.

The crystal used for data collection was 0.05 × 0.19 × 0.47 mm. Data were collected by θ—2θ scan in the range 2—110°. 2 436 Intensity data were collected by θ—2θ scan in the 2θ range 2—110°; 1 252 independent data were obtained by averaging symmetry-related reflections, of which 912, having $I > 2\sigma(I)$, were used in the analysis. Lorentz and polarization corrections were applied.

The structure was solved by direct methods and refined by anisotropic full-matrix least-squares, using the SHELX 76 system of computer programs.[6] The solution came out from the set having a combined figure-of-merit [6] R_A 0.149.

After some refinement difference Fourier successfully established the hydrogen atom positions. However, further refinement did not improve their co-ordinates, so it was found more satisfactory to fix them in the calculated positions, except for H(6) and H(7) whose co-ordinates were refined isotropically.

At the end of the refinement, carried out using $1/\sigma^2$ weights, R was 0.051 and R' 0.052 for observed reflections only, and R 0.082 and R' 0.066 for all reflections. Table 1 gives the final fractional co-ordinates with thermal parameters. Atomic scattering factors used in all calculations take into account the anomalous scattering effects following ref. 7. Structure factors, thermal parameters, and hydrogen atom geometrical parameters are deposited as Supplementary Publication No. SUP 22272 (7 pp., 1 microfiche).*

TABLE 1

Atomic fractional co-ordinates (× 10^4)

	x/a	y/b	z/c
S	528(1)	−845(2)	3 703(3)
C(2)	1 255(3)	−1 372(8)	3 342(10)
C(3)	1 453(3)	−2 865(8)	4 042(10)
C(4)	1 124(2)	−3 945(7)	4 691(9)
N(5)	535(2)	−3 753(5)	4 563(7)
C(6)	250(3)	−2 719(7)	3 440(12)
C(7)	−296(2)	−3 003(7)	4 497(10)
C(8)	103(3)	−3 794(7)	5 752(11)
O(9)	80(2)	−4 314(6)	7 160(7)
C(10)	1 323(3)	−5 446(8)	5 301(10)
O(11)	1 789(2)	−5 640(6)	5 865(8)
C(12)	900(4)	−6 757(8)	5 189(12)
C(13)	2 095(3)	−3 007(10)	3 884(13)
N(14)	−648(2)	−1 777(6)	5 014(7)
C(15)	−1 185(3)	−1 751(8)	4 470(10)
O(16)	−1 402(2)	−2 744(6)	3 603(8)
C(17)	−1 540(2)	−389(7)	5 002(10)
O(18)	−1 186(2)	818(5)	5 418(7)
C(19)	−1 438(3)	2 131(7)	5 994(10)
C(20)	−2 013(3)	2 327(8)	6 148(11)
C(21)	−2 218(3)	3 690(9)	6 758(13)
C(22)	−1 841(3)	4 830(9)	7 207(12)
C(23)	−1 275(3)	4 611(8)	7 048(11)
C(24)	−1 064(3)	3 283(7)	6 484(11)
H[C(2)]	1 317	−1 416	1 999
H[C(2)]	1 514	−504	3 885
H(6)	222(24)	−2 942(68)	2 304(93)
H(7)	−559(24)	−3 865(69)	3 994(76)
H[C(12)]	511	−6 345	4 653
H[C(12)]	825	−7 196	6 428
H[C(12)]	1 070	−7 636	4 390
H[C(13)]	2 264	−2 012	3 282
H[C(13)]	2 191	−3 993	3 113
H[C(13)]	2 278	−3 148	5 108
H(14)	−489	−898	5 818
H[C(17)]	−1 808	−52	3 941
H[C(17)]	−1 799	−689	6 046
H(20)	−2 299	1 436	5 797
H(21)	−2 658	3 905	6 829
H(22)	−1 999	5 869	7 747
H(23)	−990	5 517	7 340
H(24)	−621	3 085	6 442

All calculations were carried out on a CYBER 76 computer of Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale, Casalecchio, Bologna.

RESULTS AND DISCUSSION

The structure of the molecule is shown in Figure 1, and relevant structural parameters are collected in Figure 2 and in Tables 2 and 3. The estimated standard deviations also take into account errors in lattice constants. No correction for rigid-body motion was made since, the corrections in bond distances were shown [8] not to exceed 0.003 Å. Figure 2 shows the packing.

The molecule may be considered as being made up of five parts: a β-lactam ring fused with a dihydrothiazine

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

[6] G. M. Sheldrick, SHELX 76, program system, University of Cambridge, 1976.

[7] 'International Tables for X-Ray Crystallography,' vol. IV, Kynoch Press, Birmingham, 1974, p. 155.

[8] V. Schomaker and K. N. Trueblood, *Acta Cryst.*, 1968, **B24**, 63.

TABLE 2

Comparison of structural parameters [distances (Å) angles (°)] of Δ^3-cephem derivatives

	(4) [a]	(5) [b]	Δ/σ [e]	(6) [c]	Δ/σ [e]	(7) [d]	Δ/σ [e]
S–C(2)	1.813(8)	1.815(7)	0.19	1.827(3)	1.64	1.822(8)	0.80
S–C(6)	1.795(7)	1.787(6)	0.87	1.804(3)	1.18	1.811(8)	1.51
C(2)–C(3)	1.507(10)	1.502(8)	0.39	1.509(3)	0.19	1.523(10)	1.13
C(3)–C(4)	1.337(9)	1.359(8)	1.83	1.333(3)	0.42	1.292(10)	3.35
C(4)–N(5)	1.414(7)	1.386(7)	2.83	1.406(3)	1.05	1.433(10)	1.56
N(5)–C(6)	1.445(9)	1.458(7)	1.14	1.460(3)	1.58	1.454(10)	0.67
N(5)–C(8)	1.396(9)	1.390(8)	0.50	1.383(3)	1.37	1.379(10)	1.26
C(6)–C(7)	1.566(10)	1.570(9)	0.30	1.539(3)	2.59	1.531(10)	2.48
C(7)–C(8)	1.543(10)	1.490(10)	3.75	1.522(3)	2.01	1.537(10)	0.42
C(8)–O(9)	1.210(10)	1.214(8)	0.31	1.192(3)	1.72	1.179(10)	2.19
C(2)–S–C(6)	95.5(3)	94.4(3)	2.59	95.1(2)	1.11	95.3(4)	0.40
S–C(2)–C(3)	117.7(6)	115.6(5)	2.69	116.0(1)	2.79	115.1(7)	2.82
C(2)–C(3)–C(4)	125.7(8)	123.0(6)	2.70	123.6(2)	2.55	124.2(8)	1.33
C(3)–C(4)–N(5)	117.8(6)	120.3(5)	3.20	121.3(2)	5.53	120.5(8)	2.70
C(4)–N(5)–C(6)	125.8(7)	126.4(5)	0.70	125.2(2)	0.82	126.7(7)	0.91
N(5)–C(6)–S	109.8(5)	110.6(4)	1.25	109.4(2)	0.74	108.0(5)	2.55
C(7)–C(6)–S	113.0(5)	116.2(4)	5.00	114.9(2)	3.53	115.9(6)	3.71
C(4)–N(5)–C(8)	132.6(8)	130.1(5)	2.65	134.3(2)	2.06	131.8(8)	0.71
C(6)–N(5)–C(8)	95.1(5)	94.1(5)	1.28	94.3(2)	1.26	96.0(7)	0.98
N(5)–C(6)–C(7)	87.5(5)	86.4(4)	1.72	87.8(2)	0.56	87.1(6)	0.51
C(6)–C(7)–C(8)	84.8(5)	85.9(5)	1.56	85.9(2)	2.04	86.7(6)	2.43
C(7)–C(8)–N(5)	90.2(6)	92.1(5)	2.43	91.4(2)	1.90	89.6(8)	0.50
N(5)–C(8)–O(9)	131.0(11)	131.2(6)	0.56	131.9(2)	0.00	131.7(9)	0.14
C(7)–C(8)–O(9)	137.8(12)	136.4(6)	1.04	136.8(2)	0.82	138.7(9)	0.60
N(5), C(6), C(7)–N(5), C(7), C(8)	16.4	13.1		8.3		16.0	
N(5) · · ·C(4)–C(6)–C(8)	0.20	0.24		0.20		0.19	

Parameters [f]	Theoretical	(4)	(5)	(6)	(7) [g]
$\lvert\phi_i - \phi_{i+3}\rvert$	67	55	57	55	
$\Sigma\lvert\phi_i - \phi_{i+1}\rvert$	404	332	340	332	
$\Sigma\lvert\phi_i\rvert$	202	180	180	181	
$\Sigma\lvert\phi_i - \phi_{i+3}\rvert$	202	166	170	166	
$\Sigma\lvert(\lvert\phi_i\rvert - \lvert\phi_{i+1}\rvert)\rvert$	127	95	102	97	

[a] Present work; $R = 0.051$. [b] Ref. 1*a*; $R = 0.057$. [c] Ref. 9*a*; $R = 0.041$. [d] Ref. 9*b*; $R = 0.080$. [e] $\Delta/\sigma = (a_1 - a_2)/[\sigma^2(a_1) + \sigma^2(a_2)]^{\frac{1}{2}}$. [f] Conformational parameters following ref. 10 [g] It was not possible to calculate these angles as there is some misprint in the published co-ordinates for the carbon atom corresponding to C(6).

ring forming the characteristic moiety of cephalosporins, an acetyl substituent at C(4), and a phenoxy-group joined to the β-lactam ring by an amide central group. Comparison (Table 2) of the structural features of these groups of compound (4) with those of the corresponding ones found by crystal structure analysis in other Δ^3-cephem derivatives [1c,9] shows that these moieties have

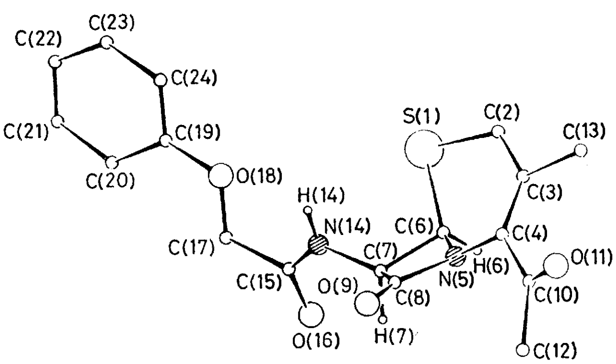


FIGURE 1 Projection of a molecule of (4)

structures whose parameters do not change relevantly in the different compounds. In particular, considering the β-lactam and the dihydrothiazine rings, the data collected in Table 2 for (4), cephaloridine hydrochloride monohydrate (5), 3-methyl-2,4-bismethoxycarbonyl-Δ^3-cephem (6), and (+)-7-benzylideneamino-7-methoxycarbonyl-4-(*p*-methoxybenzyloxycarbonyl)-Δ^3-cephem (7), indicate that there are no significant differences ($\Delta/\sigma > 3$) in bond distances and angles, except for the

[9] (*a*) E. F. Paulus, *Acta Cryst.*, 1974, **B30**, 2915; (*b*) *ibid.*, p. 2918; (*c*) D. Crowfoot Hodgkin and E. N. Maslen, *Biochem. J.*, 1961, **79**, 393.

TABLE 3

Comparison of structural parameters for the phenoxyacetamido-group

(*a*) Distances (Å)	(4)	(8) [a]	Δ/σ
C(7)–N(14)	1.429(8)	1.438(7)	0.85
N(14)–C(15)	1.348(9)	1.341(8)	0.58
C(15)–O(16)	1.229(9)	1.230(8)	1.58
C(15)–C(17)	1.529(9)	1.522(10)	0.91
C(17)–O(18)	1.398(7)	1.406(8)	0.75
O(18)–C(19)	1.383(8)	1.375(7)	0.75
Mean C–C (phenyl) [b]	1.380(4)	1.376(4)	0.88
(*b*) Angles (°)			
C(6)–C(7)–N(14)	121.2(6)	121.1(5)	0.13
C(8)–C(7)–N(14)	121.2(7)	119.2(5)	2.32
C(7)–N(14)–C(15)	118.4(6)	121.0(5)	3.33
N(14)–C(15)–O(16)	124.4(8)	122.1(6)	2.30
N(14)–C(15)–C(17)	116.6(6)	115.2(6)	1.65
O(16)–C(15)–C(17)	119.0(7)	122.6(6)	3.94
C(15)–C(17)–O(18)	109.5(5)	107.6(5)	2.55
C(17)–O(18)–C(19)	117.2(6)	117.5(4)	0.42
O(18)–C(19)–C(20)	124.2(8)	123.0(6)	1.20
O(18)–C(19)–C(24)	115.1(6)	115.3(6)	0.24
Mean C–C–C (phenyl) [b]	120.2(4)	120.1(3)	0.20
O(18)–C(17)–C(15)–N(14)	22.0(8)	−45.8(9)	56.3
O(18)–C(17)–C(15)–O(16)	−158.7(7)	137.5(8)	60.3
C(6)–C(7)–N(14)–C(15)	118.9(7)	−98.4(9)	125.2
C(8)–C(7)–N(14)–C(15)	−137.0(6)	160.0(6)	74.2
(Phenoxy–Amide)	20.4	47.9	

See footnotes to Table 2. [a] Ref. 8; R 0.056 [b] Weighted mean.

distance C(7)–C(8) which is a little shorter in (5), the angle C(3)–C(4)–N(5) which appears largely influenced by the nature of the substituent at C(4), and the angle C(7)–C(6)–S which is influenced by the S ⋯ H(14) contact. Conformational parameters following ref. 10 are also compared.

The dihedral angle N(5), C(6), C(7)–N(5), C(7), C(8) indicates a small edge-deformation for the β-lactam ring. The N(5) atom appears to be out of the plane of its three bonded carbon atoms [C(4), C(6), C(8)], as is usually found for Δ^3-cephem derivatives and exceptionally for some Δ^2-cephem derivatives [0.13 Å in (5*RS*,6*RS*,7*RS*)-7-phenylacetamido-3-methyl-4,4,7-tris-methoxycarbonyl-Δ^2-cephem].[11] Also the system of σ-bonds involving C(8) is not perfectly planar, O(9) being

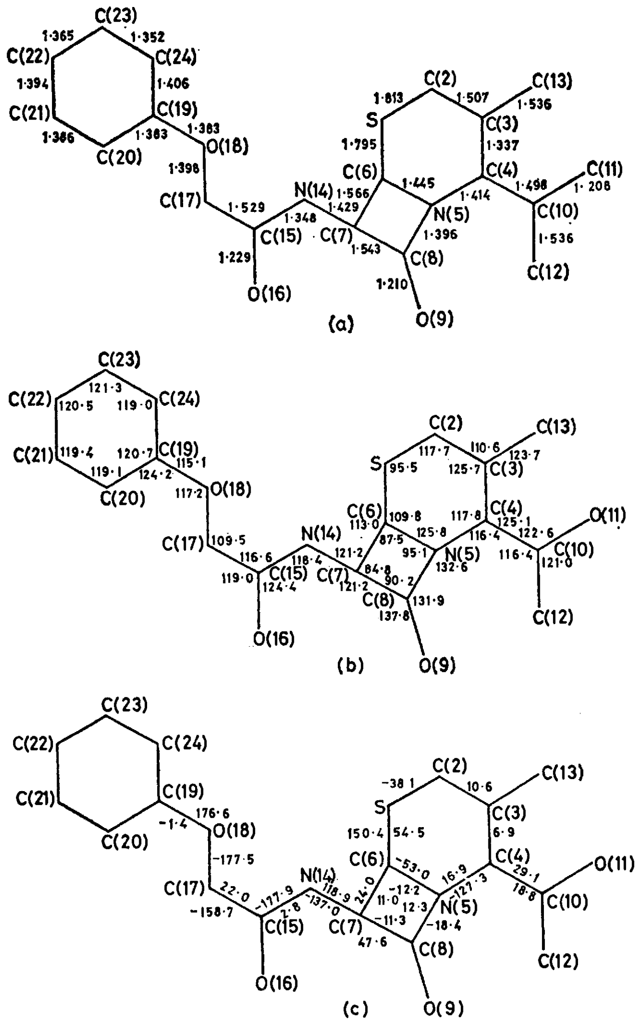
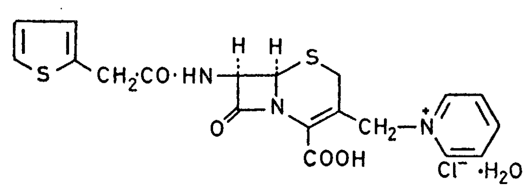
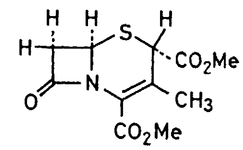


FIGURE 2 Relevant structural parameters: (a) bond distances (Å), (b) bond angles (°), (c) torsion angles (°)

0.035 Å out of the plane through N(5), C(7), C(8). Also, the high value of the lactam C=O stretching frequency (1 782 cm^{-1}) registered * for (4) was similar to that found for biologically active Δ^3-cephalosporins.[1a,c]



(5)



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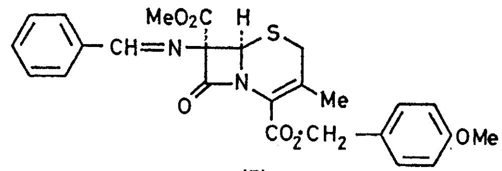
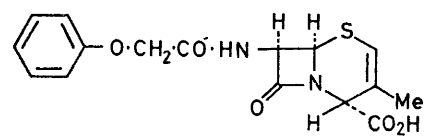


(7)



(8)

The degree of non-planarity at the lactam nitrogen together with the bond distances and the degree of planarity at C(8), as well as other properties such as the increase of the lactam C=O stretching frequency are linked to the delocalization along the C(3)–C(4)–N(5)–C(8)–O(9) system.[1c] These properties of β-lactam antibiotics have been correlated with the ease of base hydrolysis of the lactam amide bond which, according to the proposed biological mechanism of these antibiotics, seems to be strictly linked to their biological activity.[1c] Evidently in the ketone (4), which presents so many features of active cephalosporins, but which shows no biological activity, other effects must be relevant such as the presence of the acetyl group at C(4). The conformation of the six-membered sulphur-containing ring, which can be considered as half-chair, is practically the same in all the Δ^3-cephem derivatives as indicated by the data of Table 2.

In Figure 4 the half-normal probability plots [12] are represented to compare the geometry of the Δ^3-cephem characteristic moiety in different derivatives, and in

* The i.r. spectrum of (4) for determination of the β-lactamic stretching band was determined with a Perkin-Elmer 257 double beam grating spectrophotometer for *ca.* 1% w/v $CHBr_3$ solution, using the indene band at 1 915 cm^{-1} as a calibration standard; a cell of 1 mm optical length was employed.

[10] C. Foces-Foces, F. H. Cano, and S. Garcia-Blanco, *Acta Cryst.*, 1976, **B32**, 3029.

[11] D. Kobelt and E. F. Paulus, *Acta Cryst.*, 1974, **B30**, 1605.

[12] S. C. Abrahams and E. T. Keve, *Acta Cryst.*, 1971, **A27**, 157; S. C. Abrahams, *ibid.*, 1974, **B30**, 261.

Figure 5 the same plot for the phenoxyacetamido-group is considered. In these plots the ordered values of Δ/σ

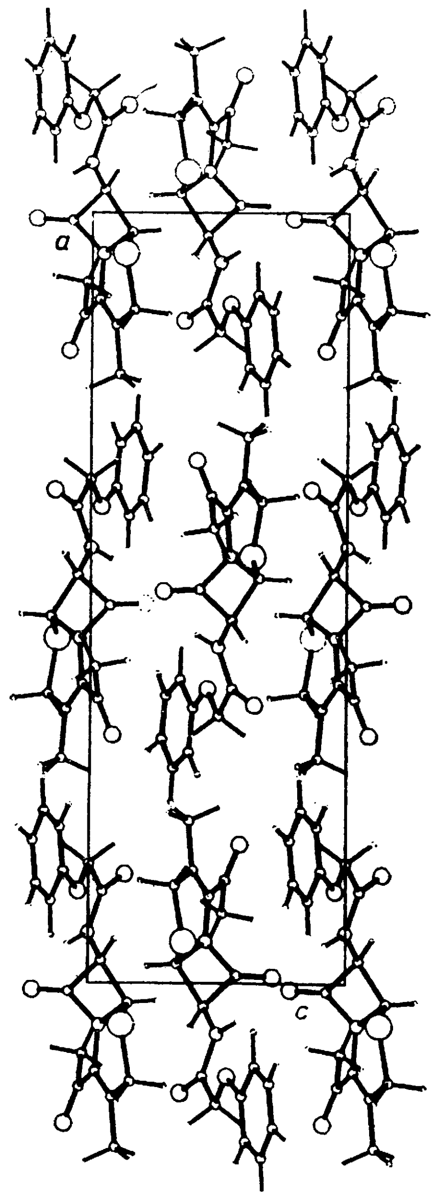


FIGURE 3 Packing in the unit cell

for all the interatomic contacts are compared with the expected values calculated for a normal distribution following the suggestion of De Camp.[13,14] Table 4 lists relevant data from these plots. From the plots of Figure 4 it appears that in the Δ^3-cephem moieties, the most relevant discrepancies are observed for non-bonding contacts involving S, C(2), C(3) and C(4), C(8), O(9) which are sensible to the conformational changes.

TABLE 4

Half-normal probability plot parameters

Compound	No. dist.	Max. $(\Delta/\sigma)_{obs.}$	Slope [a]	Intercept [a]	Δ/σ >3
(4)–(5)	36	7.05	2.56	−0.18	12
(4)–(6)	36	14.21	1.81	0.22	11
(4)–(7) [b]	27	7.94	3.21	−0.53	5
(4)–(8)	55	12.79	1.80	0.23	15

[a] Calculated for a least-squares fit to a straight line of the points with $(\Delta/\sigma)_{obs.} < 5$. [b] Excluding the carbon atom corresponding to C(6) as there is some misprint in its published co-ordinates.

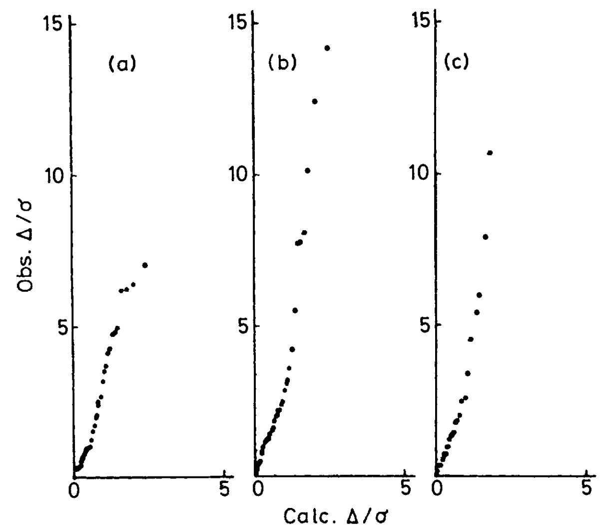


FIGURE 4 Half-normal probability plots. (a) (4)–(5), (b) (4)–(6), (c) (4)–(7). Hydrogens are excluded. In all cases standard deviations appear underestimated

Bond distances, angles, and planarity in the acetyl group are as expected. The orientation of this group which forms a dihedral angle of 24.3° with the C(3), C(4), N(5) plane is determined by the contacts O(11) ··· C(13) 2.90, O(11) ··· C(3) 2.96, C(12) ··· N(5) 2.84, C(12) ··· C(8) 3.26, and C(12) ··· O(9) 3.30 Å, which compare well with the corresponding contacts {2.99,

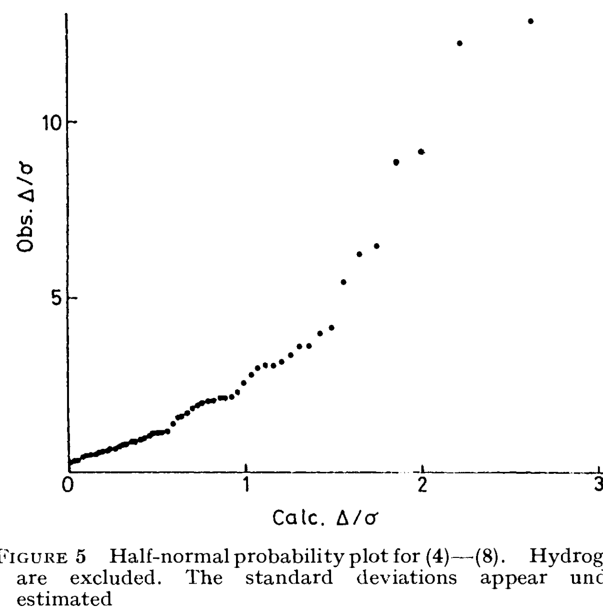


FIGURE 5 Half-normal probability plot for (4)—(8). Hydrogens are excluded. The standard deviations appear under-estimated

[13] W. H. De Camp, *Acta Cryst.*, 1973, **A29**, 148.

[14] J. Albertsson and P. M. Schultheiss, *Acta Cryst.*, 1974, **A30**, 854.

2.97, 2.80 [C(12) is oxygen], 3.28, and 3.28 Å} made by the carboxy-group in cephaloridine hydrochloride hydrate (5), even if the dihedral angle which this group forms with the C(3), C(4), N(5) plane is here greater (42.0°).

Bond distances, angles, and planarity of the central amide bridge and of the phenoxy-moiety agree well with the geometries usually found for these groups. A comparison of the structural parameters in this part of the molecule with those of the same moiety present in 3-methyl-7β-phenoxyacetamido-Δ^2-cephem-4-carboxylic acid (8)[1c] is made in Table 3. It appears that there are no significant differences in corresponding bond distances and angles, except for the angles C(7)–N(14)–C(15) and O(16)–C(15)–C(17). However, relevant differences, probably due to packing requirements, are observed for the torsion angles around C(17)–C(15) and C(7)–N(14) and for the dihedral angle between the phenoxy and the amide planes, even if the nearest internal non-bonding contacts are nearly the same. The comparison of the phenoxyacetamido groups given by the probability plot of Figure 5, shows that discrepancies are observed for non-bonding contacts involving N(14), O(16) and the phenyl group and these are due to the already mentioned changes of conformation present in the two compounds.

H(14), which has been put in the calculated position assuming complete planarity for the amido-group and symmetric C–N–H angles, lies in the field of O(18) and S from which it is 2.27 and 2.94 Å, respectively. H(7) is nearer to O(16) (2.26 Å) than to O(9) (2.96 Å).

Packing of the molecules, shown in Figure 3, is due only to normal van der Waals contacts; those <3.5 Å are: C(17) ··· $O(11^{I})$ 3.343(11), C(23) ··· $O(9^{II})$ 3.359(9), C(24) ··· $O(9^{II})$ 3.491(9), C(24) ··· $O(9^{I})$ 3.449(9), N(14) ··· $O(9^{I})$ 3.405(9), and O(18) ··· $O(9^{I})$ 3.260(7) Å, where I is at $x, y, z + 1$ and II is at $x, y + 1, z$.

[7/1955 *Received, 7th November*, 1977]