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Acta Cryst. (1979). B**35**, 1360–1363

The Structure of Chloramphenicol

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(*Received* 14 *November* 1978; *accepted* 20 *February* 1979)

Abstract

The structure of chloramphenicol, D-(−)-*threo*-2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-nitrophenethyl]acetamide, $C_{11}H_{12}Cl_2N_2O_5$, an important broad-spectrum antibiotic, has been solved by direct methods with X-ray diffraction data collected using Mo $K\alpha$ radiation. The crystals are orthorhombic, a = 7·335 (3), b = 17·552 (8), c = 22·159 (6) Å, with space group $C222_1$, and the structure has been refined by Fourier and least-squares techniques to an R of 0·069 for 940 observed reflections. The side chain exists in the 'alicyclic' form, stabilized by hydrogen bonding between the hydroxyl groups. The dichloroacetamido moiety is folded back over the phenyl ring.

Introduction

Chloramphenicol is a widely used antibiotic produced by *Streptomyces Venezuelae* (Ehrlich, Bartz, Smith, Joslyn & Burkholder, 1947) and cultures of *Streptomyces lavendulave* (Carter, Gottlieb & Anderson, 1948). It has also been obtained synthetically by several routes (Controulis, Rebstock & Crooks, 1949; Long & Troutman, 1949). The crystal structure of chloramphenicol has been shown to be isomorphous with bromamphenicol, for which two-dimensional X-ray work has been reported (Dunitz, 1952). The present work describes the three-dimensional structure of chloramphenicol.

0567-7408/79/061360-04$01.00

Experimental

Chloramphenicol in powder form was obtained from Parke–Davis (India) Ltd, Bombay. Transparent crystalline needles were grown from ethanol. Precession and Weissenberg photographs showed the crystal system to be orthorhombic, with systematic absences hkl, $h + k = 2n + 1$; $00l$, $l = 2n + 1$ indicating the space group $C222_1$. Accurate cell parameters were obtained by least-squares treatment of the 2θ values of high-angle reflections centred on a diffractometer. The crystal density was measured by a flotation technique using bromoform and *m*-xylene. The crystal data are given in Table 1.

The crystal used for data collection, 0·32 × 0·29 × 0·36 mm, was mounted on a Picker card-automated diffractometer. Data were collected employing Nb-filtered Mo $K\alpha$ radiation within the range $2\theta \leq 49°$ using the θ–2θ scanning mode operating at 2° min^{-1} in 2θ with a scan width of 1·2° in 2θ. Individual background counts were recorded at the higher 2θ limit and three check reflections were monitored periodically for

Table 1. *Crystal data of chloramphenicol*

Chemical formula: $C_{11}H_{12}Cl_2N_2O_5$	$M_r = 323·1$
Crystal system and space group: orthorhombic, $C222_1$	
a = 7·335 (3) Å	$Z = 8$
b = 17·552 (8)	$F(000) = 1328$
c = 22·159 (6)	λ(Mo $K\alpha$) = 0·71069 Å
d_m = 1·49 Mg m^{-3}	μ(Mo $K\alpha$) = 0·4741 mm^{-1}
d_c = 1·50	M.p. = 423 K

scaling purposes. Of the 1367 reflections accessed, 427 which had an intensity I(net) < I(threshold) [where I(threshold) was set as the greater quantity of 0·1 × total background or 108 counts], were treated as unobserved. Lorentz and polarization corrections were applied to the raw data of derived F's and E's.

The structure was solved with *MULTAN* (Declercq, Germain, Main & Woolfson, 1973), using 150 E's ≥ 1·40. All the non-H atoms were located in an E map computed for these data with the phases generated by the multisolution set with highest figure of merit. Successive block-diagonal least-squares refinement cycles using initially isotropic and then anisotropic thermal parameters reduced R to 0·072. The H atoms were located in difference Fourier syntheses and their positions corrected by the Booth method (Stout & Jensen, 1968); in subsequent cycles each H atom was allotted an isotropic thermal parameter equal to that of the atom to which it was attached, but neither thermal nor positional parameters were refined. In the final stages, the unobserved reflections with $F_o/F_c < 2$ were included in the least-squares calculations. Throughout, the function minimized was $\sum w(|F_o| - |F_c|)^2$ with weights, $w = 1/\sigma^2(F_o)$, and convergence was attained at an R of 0·069 for 940 observed data* with no shift being >0·25 in the final cycle. Scattering factors were taken from *International Tables for X-ray Crystallography* (1974) and computations were carried out with *MULTAN*, the NRC crystallographic program system (Ahmed, Hall, Pippy & Huber, 1973) and the IISc program set (Shiono, 1968). Final atomic parameters are presented in Tables 2 and 3.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34213 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Positional parameters* (×10⁴) *with standard deviations for non-hydrogen atoms*

	x	y	z
Cl(1)	−3068 (5)	3890 (2)	−179 (1)
Cl(2)	−1945 (7)	2629 (2)	584 (2)
O(1)	1682 (20)	1586 (6)	2880 (4)
O(2)	2978 (24)	1112 (6)	2079 (6)
O(3)	4398 (10)	4720 (4)	942 (3)
O(4)	−2107 (10)	4191 (4)	1210 (3)
O(5)	2276 (22)	5811 (6)	418 (6)
N(1)	2440 (11)	1638 (4)	2384 (4)
N(2)	624 (15)	4408 (6)	773 (4)
C(1)	3092 (17)	3872 (6)	1701 (5)
C(2)	3482 (18)	3254 (7)	1326 (6)
C(3)	3223 (20)	2505 (7)	1544 (5)
C(4)	2705 (18)	2433 (6)	2149 (6)
C(5)	2410 (15)	3035 (6)	2526 (4)
C(6)	2614 (14)	3770 (5)	2306 (4)
C(7)	3221 (13)	4672 (6)	1450 (4)
C(8)	1320 (12)	4937 (5)	1232 (4)
C(9)	−933 (15)	4082 (6)	814 (5)
C(10)	−1285 (18)	3510 (6)	282 (5)
C(11)	1315 (11)	5754 (4)	984 (3)

Table 3. *Positional parameters* (×10⁴) *of the hydrogen atoms*

	x	y	z
H(O3)	3803	5051	767
H(O5)	3281	6184	408
H(N2)	1023	4378	450
H(C2)	4262	3677	1483
H(C3)	3580	1965	1316
H(C5)	2328	2972	2980
H(C6)	2259	4261	2597
H(C7)	4005	5009	1758
H(C8)	503	4881	1569
H(C10)	−76	3350	69
H(C11)	1742	6127	1257
H(C*A*11)	−138	5811	894

Discussion

It has been suggested (Gale, Cundliffe, Reynolds, Richmond & Waring, 1972) that chloramphenicol (Fig. 1*a*) exists in an alicyclic form (Fig. 1*b*). The diagram of the structure of the compound, Fig. 2, shows that this is indeed the case in the solid state; this form is stabilized by an intramolecular hydrogen bond between O(3) and O(5) [O(3)···O(5) = 2·727 (10) Å]. The orientation of the side chain, with a *trans* arrangement of the C(7)–O(3) and C(8)–N(2) bonds, causes the dichloroacetamido group to fold back over the aromatic ring.

The bonding parameters for the structure are presented in Tables 4 and 5, with details of intermolecular approaches and mean planes being given in Tables 6 and 7. The structural geometry shows no remarkable deviation from that expected. The lattice

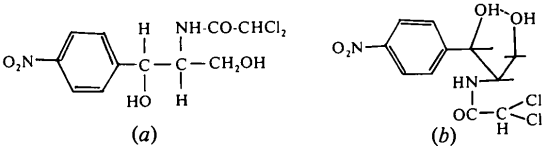

Fig. 1. (*a*) The chloramphenicol molecule. (*b*) Alicyclic ring form of chloramphenicol.

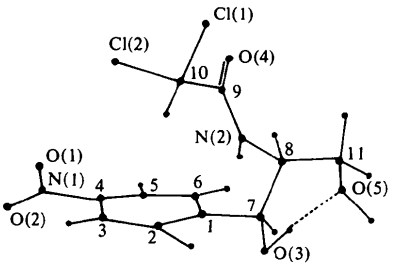

Fig. 2. Chloramphenicol viewed down the *c* axis.

packing (Fig. 3) is achieved through hydrogen bonding between O(5) and the Cl(2) atom of a molecule related by a carbon centre [O(5)···Cl(2) = 3·262 (7) Å], and between O(5) and the N(2) atom of a twofold (*a* axis) symmetry-related molecule [N(2)···O(5) = 2·929 (10) Å], with all other contacts being of the van der Waals type (Table 6).

Inhibition of protein synthesis is described as the general mode of action of chloramphenicol (Gottlieb & Shaw, 1967). It has been reported that the antibiotic binds preferentially with the 50S subunit of the ribosomal particle (Gale, Cundliffe, Reynolds, Richmond & Waring, 1972). As it combines with the subunit, the hydrogen bond between the two aliphatic hydroxyl groups might break and bind with groups having a greater affinity for H, thus inhibiting protein synthesis.

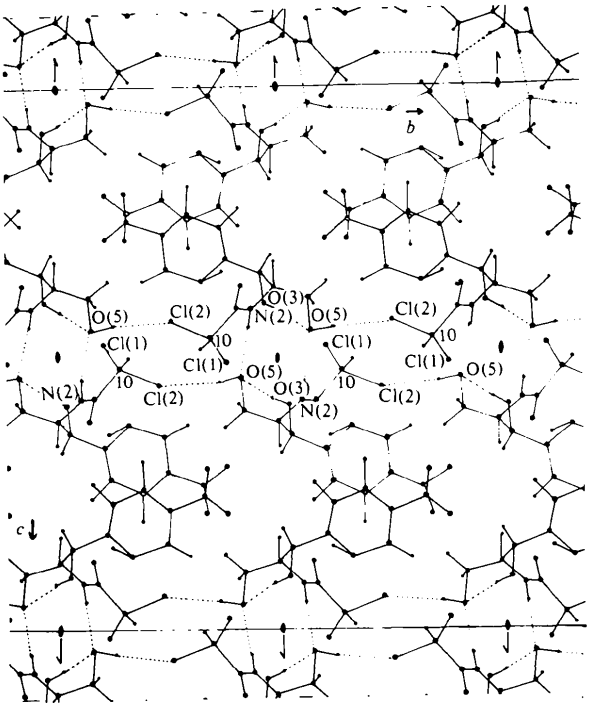

Fig. 3. Crystal packing of chloramphenicol viewed down the *a* axis.

Table 4. *Bond lengths* (Å)

C(1)–C(2)	1·396 (15)	N(1)–O(1)	1·235 (17)
C(2)–C(3)	1·414 (16)	N(1)–O(2)	1·210 (17)
C(3)–C(4)	1·398 (17)	C(8)–C(11)	1·536 (14)
C(4)–C(5)	1·364 (17)	C(11)–O(5)	1·441 (13)
C(5)–C(6)	1·388 (15)	C(8)–N(2)	1·469 (12)
C(6)–C(1)	1·397 (13)	N(2)–C(9)	1·280 (12)
C(1)–C(7)	1·513 (14)	C(9)–O(4)	1·244 (11)
C(7)–C(8)	1·547 (14)	C(9)–C(10)	1·571 (13)
C(7)–O(3)	1·422 (12)	C(10)–Cl(1)	1·789 (11)
C(4)–N(1)	1·503 (16)	C(10)–Cl(2)	1·753 (11)
O(3)–H(O3)	0·825	C(6)–H(C6)	1·017
O(5)–H(O5)	0·990	C(7)–H(C7)	1·070
N(2)–H(N2)	0·775	C(8)–H(C8)	0·963
C(2)–H(C2)	0·999	C(10)–H(C10)	1·042
C(3)–H(C3)	1·105	C(11)–H(C11)	0·946
C(5)–H(C5)	1·015	C(11)–H(C*A*11)	1·089

Table 5. *Bond angles* (°) *and their standard deviations*

O(1)–N(1)–O(2)	126·0 (14)	C(1)–C(7)–C(8)	109·7 (8)
O(1)–N(1)–C(4)	115·8 (12)	O(3)–C(7)–C(8)	106·4 (8)
O(2)–N(1)–C(4)	118·1 (13)	C(7)–C(8)–C(11)	113·2 (8)
N(1)–C(4)–C(5)	119·1 (11)	C(7)–C(8)–N(2)	109·9 (8)
N(1)–C(4)–C(3)	116·8 (11)	N(2)–C(8)–C(11)	110·0 (8)
C(3)–C(4)–C(5)	124·0 (12)	C(8)–C(11)–O(5)	112·0 (8)
C(4)–C(5)–C(6)	119·2 (11)	C(8)–N(2)–C(9)	122·8 (8)
C(5)–C(6)–C(1)	118·8 (10)	N(2)–C(9)–O(4)	126·8 (9)
C(2)–C(3)–C(4)	116·6 (11)	N(2)–C(9)–C(10)	112·2 (8)
C(1)–C(2)–C(3)	119·5 (10)	O(4)–C(9)–C(10)	120·9 (8)
C(6)–C(1)–C(2)	121·5 (10)	C(9)–C(10)–Cl(2)	108·8 (7)
C(6)–C(1)–C(7)	119·2 (9)	Cl(1)–C(10)–Cl(2)	110·2 (6)
C(2)–C(1)–C(7)	119·3 (9)	C(9)–C(10)–Cl(1)	108·1 (7)
C(1)–C(7)–O(3)	112·6 (8)		

Table 6. *Intermolecular distances* (Å) *less than* 3·6 Å

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

Cl(1)···O(3)	3·502 (8)^{ii}	O(1)···O(2)	3·519 (23)^{iv}
Cl(1)···O(5)	3·496 (9)^{ii}	C(6)···C(6)	3·60 (15)^{iv}
O(3)···O(5)	3·518 (10)^{ii}	O(1)···O(1)	2·987 (19)^{iv}
O(5)···O(5)	3·397 (9)^{ii}	O(1)···N(1)	3·081 (22)^{iv}
O(2)···O(2)	3·505 (24)^{iv}	O(1)···C(4)	3·546 (20)^{iv}
O(5)···C(10)	3·263 (13)^{ii}	C(5)···C(5)	3·537 (18)^{iv}
O(4)···C(5)	3·467 (14)^{iv}	O(2)···C(11)	3·503 (19)^{v}
O(4)···C(6)	3·391 (11)^{iv}	O(1)···C(11)	3·26 (15)^{viii}

Table 7. *Least-squares planes*

The equations are of the form $px + qy + rz = d$, where x,y,z and d are in Å.

Plane	Atoms in plane	Equation of plane
1	C(1), C(2), C(3), C(4), C(5), C(6), C(7)	$0·8772x - 0·0069y + 0·4802z = 3·8566$
2	O(1), O(2), N(1)	$0·9546x + 0·0109y + 0·2977z = 3·3093$
3	O(3), C(7), C(8), C(11), O(5)	$0·6951x + 0·0055y + 0·7189z = 3·1741$

Deviations from the least-squares planes

Plane	Atom	Deviation (Å)	Plane	Atom	Deviation (Å)
1	C(1)	−0·102	2	O(1)	−0·199
	C(2)	−0·245		O(2)	0·176
	C(3)	−0·169		N(1)	0·001
	C(4)	0·142	3	O(3)	0·614
	C(5)	0·344		C(7)	0·822
	C(6)	0·234		C(8)	−0·491
	C(7)	−0·298		C(11)	−0·882
				O(5)	−1·292

We thank Professor M. A. Viswamitra, Indian Institute of Science, Bangalore, for his interest in the work and his group for their kind help with the computer programming. We thank Professor K. N. Kuchela, Head of the Department of Physics, Bangalore University, for his encouragement. Michael Post thanks the National Research Council of Canada for

the award of a Research Associateship, and D. S. Sake Gowda wishes to acknowledge the award of the research grant by the Indian Council of Medical Research, New Delhi.

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Acta Cryst. (1979). B**35**, 1363–1372

Crystal and Molecular Structure of *p*-Methoxybenzyl 2α-Methyl-2β-[(*R*)-acetoxy(methoxy)methyl]-6β-phenoxyacetamidopenam-3α-carboxylate

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(*Received* 12 *June* 1978; *accepted* 25 *January* 1979)

Abstract

The title compound, $C_{27}H_{30}N_2O_9S$, crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 20·526 (5), b = 12·756 (2), c = 10·298 (3) Å, Z = 4. The structure has been solved by direct methods and refined by a least-squares procedure to a conventional R value of 0·033 (absolute configuration) for 2562 observed independent reflections. A comparison of several known structures of penicillin derivatives is made. Only small differences are observed for the characteristic moiety of this class of compounds. In the title compound the thiazolidine ring exhibits slight puckering, the C(3) atom is 0·39 Å out of the plane through the remaining four atoms. The N atom of the β-lactam ring is 0·37 Å out of the plane of its ligand C atoms. The phenoxymethyl moiety is compared with that of other penicillin and cephalosporin derivatives. Packing results from normal van der Waals contacts.

0567-7408/79/061363-10$01.00

Introduction

In recent years the study of interconversion reactions of penicillins and cephalosporins has received considerable attention (Cooper & Spry, 1972; Cooper, Hatfield & Spry, 1973; Kukolja, Lammert, Gleissner & Ellis, 1975; Tanida, Tsuji, Tsushima, Ishitobi, Irie, Yano, Matsumura & Tori, 1975). This interconversion is usually supposed to occur through a mechanism implying the formation and the rearrangement of thiiranium ion intermediates (Cooper & Spry, 1972; Cooper, Hatfield & Spry, 1973; Kukolja *et al.*, 1975; Barton, Comer, Greig, Lucente, Sammes & Underwood, 1970).

As a continuation of our studies of the chemistry of the dihydrothiazine ring moiety of cephalosporins (Balsamo, Crotti, Domiano, Macchia, Macchia, Nannini & Rosai, 1978; Domiano, Nardelli, Balsamo, Macchia, Macchia & Meinardi, 1978), we started an