Crystal Structure and Relative Configuration of the *N*-Acetyl-γ-lactone of the Antifungal Antibiotic Thermozymocidin

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An *X*-ray crystal structure determination of (1), the acetylation product of thermozymocidin [$C_{23}H_{39}NO_6$, ortho-rhombic, space group $P2_12_12_1$, $a = 41.477(9)$, $b = 10.753(5)$, $c = 5.543(1)$ Å, $Z = 4$, direct methods, final R 0.062 for 1 124 independent reflections], has established the relative configuration of the asymmetric carbon atoms of this antifungal antibiotic. The structure analysis shows a large thermal vibration in the long aliphatic chain which can explain the systematic shortening of the observed bond distances. The conformations of the carbon chain and of the lactone ring are discussed.

THERMOZYMOCIDIN is a new antifungal antibiotic isolated from a thermophilic mould [1] for which chemical and physical evidence suggested structure (1), 2-amino-3,4-dihydroxy-2-hydroxymethyl-14-oxoeicos-6-enoic acid.[2]

Incorporation experiments with [^{14}C]-labelled substrates [3] and [1-^{13}C]acetate [4] revealed that the carbon skeleton of this microbial metabolite is assembled from L-serine and an acetogenine, probably a linear C_{18} carboxylic acid. The relative configuration of the asymmetric carbon atoms could not be established by spectroscopic methods.[2] An *X*-ray diffraction analysis was

scanwidth 1.4°, and background count 15 s at the start and finish of each scan. 1 853 reflections having $h, k, l \geqslant 0$ and $3° < \theta < 55°$ were obtained, of which 1 124 with $I > 3\sigma$ were used in the structure determination and refinement.

Crystal Data.—$C_{23}H_{39}NO_6$, $M = 425.6$, Orthorhombic, $a = 41.477(9)$, $b = 10.753(5)$, $c = 5.543(1)$ Å, $U = 2\,472(1)$ Å^3, $Z = 4$, $D_c = 1.14$ g cm^{-3}, $F(000) = 928$. Cu-K_α radiation, $\lambda = 1.541\,78$ Å; μ(Cu-K_α) = 6.7 cm^{-1}. Space group $P2_12_12_1$ (No. 19).

Structure Determination and Refinement.—Intensities were corrected for Lorentz and polarization effects but not for absorption ($\mu R < 0.2$).

(1)

(1a)
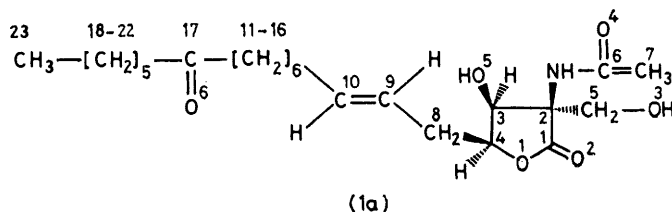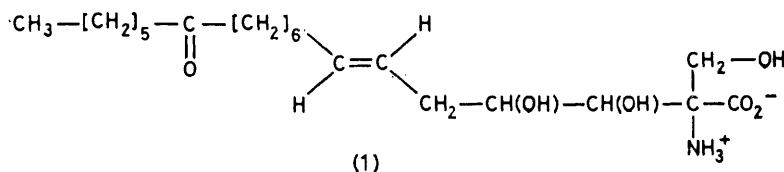
therefore performed on a stable and crystallizable thermozymocidin derivative, the *N*-acetyl-γ-lactone. On the basis of the obtained results we established the configuration shown in (1a).

EXPERIMENTAL

Crystallographic Measurements.—A roughly cubic crystal, *ca.* 0.3 mm in size, sealed in a low-absorption glass capillary, was used for *X*-ray measurements. Unit-cell parameters and integrated intensities were measured by use of a Philips PW 1100 single-crystal automatic diffractometer with graphite-monochromated Cu-K_α radiation. Unit-cell and crystal symmetries were determined by use of the standard control program of the PW 1100 system [5] with a randomly oriented crystal. Integrated intensities were measured by the ω-scan method with scan speed of 0.04° s^{-1},

The structure was solved by direct methods, with the set of programs SIG2, SYMBAD, TANFOR prepared by Destro and co-workers.[6] The new multisolution version of TANFOR gave 373 phases, and from the subsequent *E* map all non-hydrogen atoms were located. Their positional and thermal parameters were refined by block-diagonal-matrix least-squares methods to R 0.128 (4 isotropic cycles) and R 0.076 (4 anisotropic cycles). The subsequent difference electron-density map was not quite clear: broad peaks near most carbon atoms of the aliphatic chain indicated the presence of some structural disorder of a conformational kind (also evident from the exceedingly large values for the thermal parameters). The positions of the 39 hydrogen atoms were therefore derived both from the difference map and from geometrical considerations. In the final cycles of least-squares refinement, hydrogen atoms were excluded from the refinement but not from the

structure-factor calculation; their isotropic thermal factors were assumed to be equal to the mean of the carbon atoms to which they were bonded. Convergence was achieved at R 0.062 (mean shift-to-error ratio 0.34). The weighting scheme $w = 1/[1 + 0.055F_o]$ gave a uniform mean value of $w(F_o - F_c)^2$ for various intervals of F_o.

Atomic scattering factors were taken from ref. 7; the

TABLE 1

Non-hydrogen atom fractional co-ordinates ($\times 10^4$), with estimated standard deviations in parentheses

	x/a	y/b	z/c
C(1)	149(1)	3 062(5)	7 073(10)
C(2)	198(1)	3 093(5)	9 804(10)
C(3)	451(1)	4 149(5)	10 131(10)
C(4)	605(1)	4 268(5)	7 620(11)
C(5)	331(1)	1 829(5)	10 513(10)
C(6)	−339(2)	4 035(5)	10 370(11)
C(7)	−638(2)	3 999(6)	11 752(13)
C(8)	684(1)	5 551(6)	6 719(11)
C(9)	949(2)	6 158(7)	8 121(16)
C(10)	1 140(3)	6 821(9)	7 903(21)
C(11)	1 404(2)	7 455(7)	9 254(21)
C(12)	1 505(2)	8 676(7)	8 167(18)
C(13)	1 792(2)	9 289(7)	9 491(17)
C(14)	1 922(2)	10 411(7)	8 182(18)
C(15)	2 203(4)	11 012(7)	9 476(19)
C(16)	2 334(2)	12 126(8)	8 160(20)
C(17)	2 594(2)	12 855(7)	9 411(18)
C(18)	2 764(2)	13 834(8)	8 062(19)
C(19)	3 015(2)	14 560(7)	9 208(21)
C(20)	3 184(2)	15 515(8)	7 784(21)
C(21)	3 424(2)	16 312(8)	8 909(22)
C(22)	3 593(3)	17 196(10)	7 564(27)
C(23)	3 797(2)	18 081(9)	8 698(24)
N	−103(1)	3 252(4)	11 046(8)
O(1)	373(1)	3 723(3)	5 918(7)
O(2)	−55(1)	2 467(3)	6 021(7)
O(3)	605(1)	1 506(3)	9 095(8)
O(4)	−301(1)	4 712(4)	8 535(8)
O(5)	307(1)	5 287(3)	10 998(7)
O(6)	2 643(2)	12 712(6)	11 582(15)

least-squares refinement program given in ref. 8 was used. Table 1 reports final positional parameters for the 30 heavy atoms with their estimated standard deviations. Hydrogen

TABLE 2

Fractional co-ordinates ($\times 10^3$) for hydrogen atoms; atoms are numbered according to the carbon atom to which they are attached and distinguished by the last number

	x/a	y/b	z/c		x/a	y/b	z/c
H(31)	62	385	1 142	H(152)	239	1 036	979
H(41)	82	372	760	H(161)	243	1 178	647
H(51)	40	184	1 236	H(162)	214	1 272	773
H(52)	15	114	1 027	H(181)	288	1 344	648
H(71)	−62	334	1 325	H(182)	259	1 450	734
H(72)	−83	368	1 069	H(191)	290	1 505	1 075
H(73)	−70	486	1 249	H(192)	319	1 395	1 002
H(81)	76	553	488	H(201)	331	1 503	628
H(82)	47	613	681	H(202)	301	1 609	684
H(91)	94	585	999	H(211)	330	1 682	1 035
H(101)	115	711	605	H(212)	360	1 573	984
H(111)	133	762	1 105	H(221)	374	1 670	631
H(112)	161	686	933	H(222)	342	1 771	650
H(121)	158	851	634	H(231)	392	1 872	761
H(122)	131	927	812	H(232)	398	1 764	983
H(131)	170	961	1 123	H(233)	366	1 864	1 002
H(132)	197	864	982	H(11) *	−14	277	1 250
H(141)	201	1 010	650	H(33) †	68	70	962
H(142)	174	1 107	791	H(55) †	34	591	977
H(151)	212	1 133	1 122				

* Amino-group hydrogen. † Hydroxy-hydrogen.

graphic axis; molecular dimensions are given in Table 3. The relative configuration of the three asymmetric centres C(2), C(3), and C(4) is illustrated in Figure 1: atoms C(8), O(5), and N lie on the same side with respect to the five-membered ring (see also Table 4). The *trans*-configuration of the double bond between C(9) and C(10), inferred from i.r. spectra,[2] is confirmed.

Some bond lengths (Table 3) are anomalously short, especially in the hydrocarbon chain: the mean C–C bond distance for atoms C(10) to C(23) is 1.48 Å; the C(9)–C(10) double bond distance is 1.079 Å. Relatively short bond lengths and large valency angles have already been reported for long hydrocarbon chains [9-12] and can be explained as the result of considerable thermal and/or

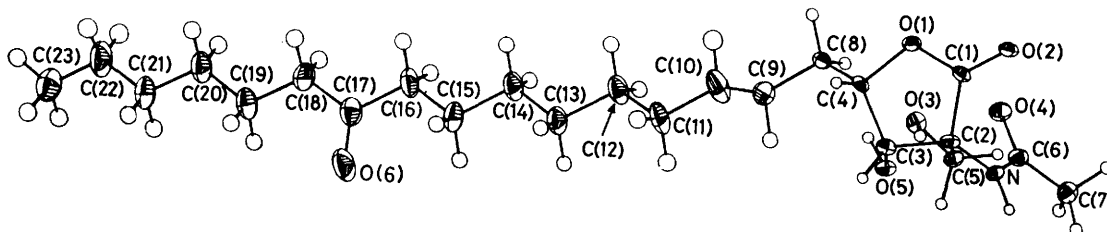

FIGURE 1　The molecule of thermozymocidin-N-acetyl-γ-lactone (1) shown along one non-crystallographic axis in an arbitrary absolute configuration. The drawing, showing the thermal-motion ellipsoids, was obtained by use of ORTEP

atom co-ordinates are listed in Table 2. Lists of observed and calculated structure factors and thermal parameters are deposited in Supplementary Publication No. SUP 22476 (15 pp.).*

DISCUSSION

Figure 1 shows a projection, together with the atom numbering scheme, of the resulting molecular model of thermozymocidin-N-acetyl-γ-lactone in an arbitrary absolute configuration, viewed along one non-crystallo-

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

librational motion; actually the refinement of the present structure led to anisotropic temperature parameters >10 Å^2 (up to 16 Å^2) for several carbon atoms in the chain. Figure 1, drawn by the ORTEP program, gives the graphic representation of the thermal-motion ellipsoids; as for N-tetracosanoylphytosphingosine, described in ref. 9, the carbon atoms exhibit a large motion in the planes which are normal to the chain axis, but a small one in the chain direction. If the mathematical model of atomic independent motion is used and the method for approximating the mean interatomic distances given in ref. 13 is applied, the observed C–C

TABLE 3

Molecular dimensions, with estimated standard deviations in parentheses. Those involving hydrogen atoms are not listed

(a) Bond distances (Å)

C(1)–C(2)	1.528(8)	C(9)–C(10)	1.079(14)
C(2)–C(3)	1.556(8)	C(10)–C(11)	1.489(15)
C(3)–C(4)	1.538(8)	C(11)–C(12)	1.504(12)
C(4)–O(1)	1.470(7)	C(12)–C(13)	1.545(12)
O(1)–C(1)	1.334(7)	C(13)–C(14)	1.508(12)
C(1)–O(2)	1.210(7)	C(14)–C(15)	1.512(12)
C(2)–C(5)	1.519(8)	C(15)–C(16)	1.505(12)
C(5)–O(3)	1.426(7)	C(16)–C(17)	1.500(12)
C(2)–N	1.433(7)	C(17)–O(6)	1.230(13)
N–C(6)	1.345(7)	C(17)–C(18)	1.472(12)
C(6)–C(7)	1.460(9)	C(18)–C(19)	1.450(13)
C(6)–O(4)	1.261(7)	C(19)–C(20)	1.467(13)
C(3)–O(5)	1.443(6)	C(20)–C(21)	1.462(13)
C(4)–C(8)	1.503(8)	C(21)–C(22)	1.405(15)
C(8)–C(9)	1.496(11)	C(22)–C(23)	1.422(16)

(b) Valency angles (°)

C(1)–C(2)–C(3)	102.8(7)	C(3)–C(4)–C(8)	117.9(9)
C(2)–C(3)–C(4)	103.7(7)	O(1)–C(4)–C(8)	107.1(7)
C(3)–C(4)–O(1)	105.9(7)	C(4)–C(8)–C(9)	112.7(10)
C(4)–O(1)–C(1)	111.2(8)	C(8)–C(9)–C(10)	140.7(28)
O(1)–C(1)–C(2)	111.8(8)	C(9)–C(10)–C(11)	142.1(32)
C(2)–C(1)–O(2)	125.6(10)	C(10)–C(11)–C(12)	113.7(15)
O(1)–C(1)–O(2)	122.5(9)	C(11)–C(12)–C(13)	113.4(12)
C(1)–C(2)–C(5)	106.5(8)	C(12)–C(13)–C(14)	112.9(12)
C(3)–C(2)–C(5)	112.2(8)	C(13)–C(14)–C(15)	112.9(12)
C(2)–C(5)–O(3)	111.4(7)	C(14)–C(15)–C(16)	112.9(12)
C(1)–C(2)–N	111.4(8)	C(15)–C(16)–C(17)	116.8(13)
C(5)–C(2)–N	107.4(7)	C(16)–C(17)–C(18)	118.8(15)
C(3)–C(2)–N	116.3(8)	C(17)–C(18)–C(19)	120.5(15)
C(2)–N–C(6)	125.0(11)	C(18)–C(19)–C(20)	118.6(15)
N–C(6)–C(7)	117.2(10)	C(19)–C(20)–C(21)	120.3(15)
N–C(6)–O(4)	119.7(9)	C(20)–C(21)–C(22)	121.1(18)
C(7)–C(6)–O(4)	123.0(12)	C(21)–C(22)–C(23)	121.2(19)
C(2)–C(3)–O(5)	112.3(7)	C(16)–C(17)–O(6)	120.4(17)
C(4)–C(3)–O(5)	113.8(8)	C(18)–C(17)–O(6)	120.4(17)

(c) Selected torsion angles (°)

C(1)–C(2)–N–C(6)	42.0
C(2)–N–C(6)–C(7)	−175.3
C(1)–C(2)–C(5)–O(3)	−51.9
C(5)–C(2)–N–C(6)	158.3
C(3)–C(4)–C(8)–C(9)	−67.8
C(4)–C(8)–C(9)–C(10)	−150.4
C(8)–C(9)–C(10)–C(11)	−178.8
C(9)–C(10)–C(11)–C(12)	155.9
C(10)–C(11)–C(12)–C(13)	176.6
C(11)–C(12)–C(13)–C(14)	−171.6
C(12)–C(13)–C(14)–C(15)	−180.0
C(13)–C(14)–C(15)–C(16)	−179.7
C(14)–C(15)–C(16)–C(17)	−174.7
C(15)–C(16)–C(17)–C(18)	−170.9
C(16)–C(17)–C(18)–C(19)	−179.9
C(17)–C(18)–C(19)–C(20)	−179.2
C(18)–C(19)–C(20)–C(21)	−176.6
C(19)–C(20)–C(21)–C(22)	−177.7
C(20)–C(21)–C(22)–C(23)	−171.7

bond lengths can be increased by 0.2 Å at most. Although this model can scarcely be applied to the present problem (partly because the thermal vibration could be attributed, to some extent, to the structural disorder already mentioned), our conclusion is that the observed short distances are unrealistic. However, no attempt has been made to ' correct ' the atomic positions owing to the molecule size, its intrinsic non-rigidity, and the trivial nature of the actual bond lengths.

The zig-zag carbon chain from C(10) to C(23) is roughly planar within 0.18 Å. However, on considering

the two saturated fragments from C(10) to C(17) and from C(17) to C(23), two least-squares planes angled by 19° are obtained, with carbon atom deviations within 0.10 and 0.08 respectively [planes (I) and (II) of Table 4]; O(6) belongs to the second plane. The torsion angles about the C(8)–C(9) and C(10)–C(11) bonds (−150 and 156° respectively) show an *anti*-periplanar conformation [14] both between C(4) and C(10) and between C(9) and C(12). Inspection of the list of torsion angles (Table 3) also indicates a staggered-type conformation about the C(4)–C(8) bond, the deviation being ±8°. We want to stress that the foregoing discussion applies to the average structure of the zig-zag molecular fragment, whereas the local, instantaneous conformations may deviate appreciably from the average, as is clearly suggested by the anomalously large values of the anisotropic thermal parameters. The geometry of the lactone

TABLE 4

Deviations (Å) of relevant atoms from least-squares planes

Plane (I): Hydrocarbon fragment, C(10)—(17)

C(10) −0.077, C(11) −0.047, C(12) 0.109, C(13) 0.064, C(14) 0.029, C(15) −0.024, C(16) −0.068, C(17) 0.003, O(6) 0.373, C(4) −0.234, C(8) 0.083, C(9) 0.106

Plane (II): Hydrocarbon fragment, C(17)—(23)

C(17) 0.010, C(18) 0.061, C(19) −0.049, C(20) −0.010, C(21) −0.044, C(22) −0.056, C(23) 0.088, O(6) −0.010

Plane (III): Lactone ring, C(1), C(2), C(4), O(1)

C(1) −0.006, C(2) 0.003, C(3) 0.347, C(4) −0.003, O(1) 0.006, O(2) −0.085

Plane (IV): Amino-group, C(2), N, C(6), C(7)

C(2) −0.026, N 0.030, C(6) 0.019, C(7) −0.023

ring is close to the so-called C_s or ' envelope ' form, which corresponds to a real energy well and which is one of the preferred puckered conformations assumed by cyclopentane derivatives containing hetero-atoms too.[14-16] In fact, as expected, C(1), C(2), C(4), and O(1) lie in a plane to within 0.006 Å, whereas C(3) is 0.35 Å out (Table 4); O(2) deviates from plane (III) by 0.085 Å. Bond distances and angles are as expected for a lactone ring.[17]

The amide group is almost planar [plane (IV)] and its geometry is in a good agreement with that described for other structures.[17]

Figure 2 shows the molecular packing. The molecules are arranged ' head-to-tail ' in pairs, thus allowing the best packing among lactonic fragments; such a disposition has been previously found for similar structures.[18] Notice that the equidistance among the parallel aliphatic chains is not due to crystallographic constraints; owing to such a regular arrangement, all intermolecular contacts involving the carbon atoms are close to the van der Waals distances. The short intermolecular contacts O(2) · · · O(5) 2.80 and O(3) · · · O(4) 2.73 Å may suggest the formation of hydrogen bonds which would, however, be rather weak owing to the large thermal motion of the atoms involved.
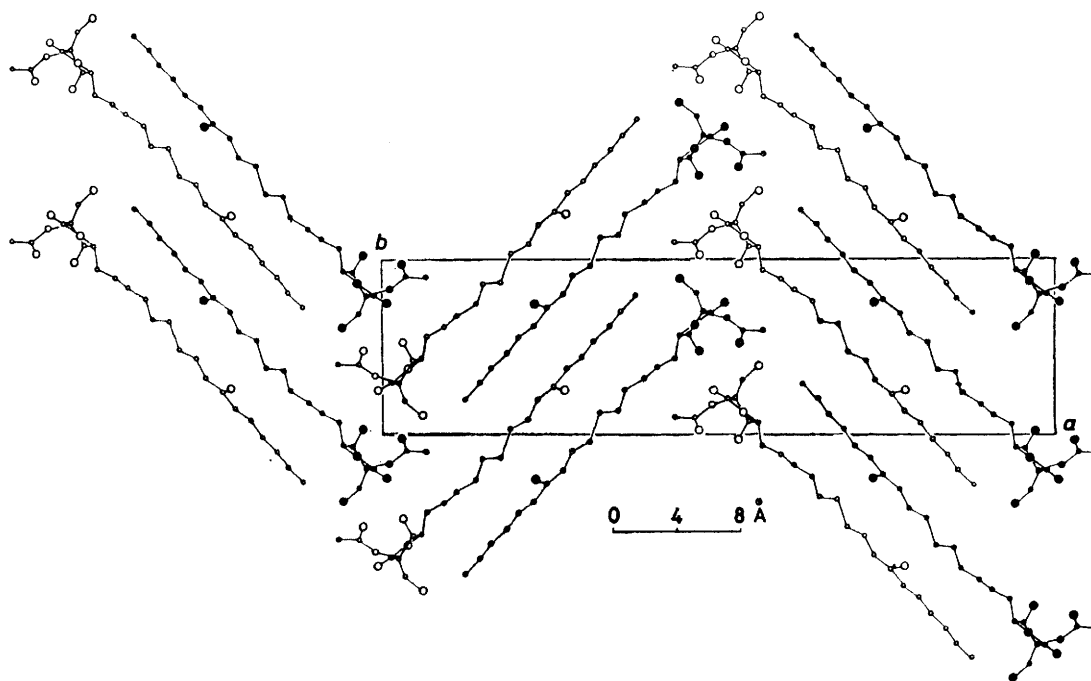
FIGURE 2 Molecular packing of (1) as seen along the c axis

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