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The β-Form of Chloramphenicol Palmitate

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Abstract. $C_{27}H_{41}O_6N_2Cl_2$, M.W. 560·5. Orthorhombic, $P2_12_12_1$, $a=7{\cdot}76$ (4), $b=52{\cdot}6$ (3), $c=7{\cdot}40$ (4) Å, $U=3021$ Å^3, $Z=4$, $D_x=1{\cdot}232$ g cm^{-3}. The final R value was 0·137 for 1249 reflexions. The packing of the hydrocarbon long chains is of the $O_\perp$ type and the chains make an angle of 45° with the basal plane (010).

Introduction. Chloramphenicol palmitate (CMP) has two crystalline polymorphic forms, α and β (Tamura & Kuwano, 1961). The α form is unstable at room temperature and gradually transforms to β on storage but it gives higher concentration of chloramphenicol in blood serum than β in the case of oral doses. This difference is considered to be caused by the difference in the rate of hydrolysis of CMP *in vivo* between the two forms (Aguiar, Krc, Kinkel & Samyn, 1967; Aguiar & Zelmer, 1969). The physical properties of these crystals, such as the dissolution behaviour and the rate of the transformation were investigated by Aguiar *et al.* (1967). The present study was initiated to elucidate the structural difference between the α and β forms, but since crystals of the α form suitable for X-ray analysis could not be obtained we describe the result of the structure determination of the β form alone.

The crystals of CMP-β were grown from a dilute

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Table 1. *Atomic parameters* ($\times 10^4$)

Temperature factors are of the form $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	11444 (8)	998 (1)	2733 (9)	142 (13)	3 (0)	139 (15)	−3 (2)	−42 (13)	−2 (2)
Cl(2)	8935 (10)	1186 (1)	150 (10)	259 (18)	4 (0)	214 (19)	−1 (2)	−73 (18)	8 (2)
C(1)	9933 (31)	916 (3)	1101 (27)	213 (55)	3 (1)	96 (46)	−2 (5)	−113 (44)	−6 (5)
C(2)	8609 (29)	731 (4)	1701 (33)	75 (45)	2 (1)	183 (62)	−8 (5)	90 (48)	−2 (6)
C(3)	6880 (30)	537 (4)	4081 (36)	119 (51)	4 (1)	166 (69)	−8 (6)	−13 (49)	4 (7)
C(4)	5109 (37)	673 (4)	3955 (36)	262 (64)	3 (1)	152 (67)	12 (6)	−80 (62)	0 (7)
C(5)	7367 (26)	474 (4)	6065 (29)	41 (42)	4 (1)	131 (50)	6 (5)	2 (40)	−13 (6)
C(6)	8830 (27)	305 (3)	6107 (25)	115 (43)	2 (1)	134 (42)	−5 (5)	71 (41)	3 (4)
C(7)	8611 (34)	42 (4)	5675 (31)	172 (54)	3 (1)	68 (56)	−4 (6)	34 (51)	1 (6)
C(8)	10021 (33)	−115 (4)	5616 (32)	168 (55)	4 (1)	69 (57)	−2 (6)	92 (49)	2 (6)
C(9)	11735 (29)	−29 (4)	6092 (29)	170 (56)	3 (1)	44 (52)	5 (6)	8 (45)	6 (5)
C(10)	11958 (29)	228 (4)	6469 (32)	101 (51)	4 (1)	69 (56)	2 (6)	2 (46)	4 (6)
C(11)	10536 (28)	389 (4)	6504 (26)	162 (52)	3 (1)	89 (45)	−3 (5)	26 (38)	−6 (5)
C(12)	4395 (31)	959 (4)	6492 (32)	148 (53)	4 (1)	105 (57)	−1 (6)	7 (47)	4 (6)
C(13)	4884 (43)	1236 (5)	6926 (42)	292 (77)	5 (1)	217 (83)	2 (8)	−20 (70)	−10 (8)
C(14)	4078 (42)	1271 (4)	8864 (40)	318 (79)	3 (1)	233 (80)	−10 (8)	158 (75)	0 (8)
C(15)	4661 (45)	1541 (4)	9483 (38)	437 (94)	3 (1)	112 (68)	1 (8)	121 (66)	−5 (7)
C(16)	4031 (50)	1601 (5)	11458 (43)	417 (96)	4 (1)	269 (89)	−12 (9)	178 (89)	−11 (8)
C(17)	4646 (51)	1878 (5)	11904 (46)	474 (110)	5 (1)	244 (96)	−8 (10)	76 (84)	−17 (9)
C(18)	3941 (45)	1945 (4)	13917 (38)	359 (79)	2 (1)	197 (71)	−3 (7)	33 (73)	−2 (7)
C(19)	4617 (50)	2185 (5)	14563 (47)	428 (103)	5 (1)	278 (92)	−3 (10)	152 (85)	−5 (9)
C(20)	3900 (43)	2277 (4)	16433 (32)	350 (73)	4 (1)	58 (58)	0 (8)	48 (65)	−6 (6)
C(21)	4599 (48)	2529 (5)	16964 (49)	389 (97)	5 (1)	365 (108)	−15 (9)	45 (84)	−37 (10)
C(22)	3910 (33)	2599 (4)	18957 (34)	138 (53)	5 (1)	172 (64)	−3 (6)	−29 (59)	−24 (7)
C(23)	4579 (42)	2865 (5)	19615 (43)	308 (82)	4 (1)	243 (82)	−2 (8)	64 (70)	−14 (8)
C(24)	3803 (41)	2929 (4)	21500 (35)	260 (69)	4 (1)	106 (62)	−7 (8)	67 (65)	1 (7)
C(25)	4631 (48)	3173 (5)	22221 (48)	418 (98)	3 (1)	275 (90)	−1 (9)	−55 (84)	3 (9)
C(26)	3820 (49)	3239 (7)	24067 (53)	294 (87)	9 (2)	370 (112)	2 (11)	123 (101)	−4 (12)
C(27)	4537 (53)	3491 (6)	24868 (50)	459 (115)	6 (2)	279 (100)	7 (11)	−62 (93)	−15 (10)
O(1)	7741 (20)	618 (2)	552 (20)	188 (37)	3 (1)	68 (38)	−7 (4)	48 (32)	−6 (4)
O(2)	5180 (18)	937 (2)	4722 (19)	99 (30)	2 (1)	92 (34)	−2 (3)	−32 (29)	−3 (4)
O(3)	7785 (22)	709 (3)	6952 (21)	212 (39)	4 (1)	89 (39)	1 (4)	−24 (32)	−3 (4)
O(4)	3725 (27)	794 (3)	7090 (26)	278 (46)	5 (1)	228 (48)	−8 (5)	40 (47)	1 (5)
O(5)	12853 (23)	−437 (3)	5926 (29)	205 (42)	4 (1)	302 (55)	2 (5)	−4 (42)	−7 (6)
O(6)	14552 (24)	−112 (3)	6271 (31)	171 (44)	7 (1)	390 (67)	−6 (5)	−56 (47)	−24 (7)
N(1)	8270 (24)	717 (3)	3404 (27)	153 (43)	2 (1)	145 (48)	−3 (4)	33 (38)	6 (5)
N(2)	13149 (28)	−203 (4)	6141 (27)	209 (52)	5 (1)	86 (52)	−5 (6)	−8 (45)	−6 (6)

xylene solution by slow evaporation at room temperature. They were colourless prisms elongated along the *c* axis. The lattice constants were determined by the three equatorial precession photographs taken with Cu $K\alpha$ radiation. The intensity data were collected on multiple-film equi-inclination Weissenberg photographs of the 0 to 5th layers around both the *b* and *c* axes and measured by a Narumi microdensitometer. The dimensions of the crystals were about $0{\cdot}3\times0{\cdot}4\times0{\cdot}7$ mm. The total number of observed reflexions was 1249 out of about 1500 possible reflexions within the 2θ angle of 100°. X-ray measurement on a small flaky crystal of CMP-α gave the following crystal data: CMP-α, monoclinic, $P2_1$, $a=36{\cdot}3$ (7), $b=16{\cdot}8$ (4), $c=5{\cdot}18$ (1) Å, $\beta=90{\cdot}5$ (5)°, $U=3157$ Å^3, $Z=4$, $D_x=1{\cdot}179$ g cm^{-3}.

A clue to the structure determination of CMP-β was obtained by phasing the *F*'s based on the positions of the two chlorine atoms ($R=0{\cdot}55$). Refinement was carried out by the method of full-matrix least-squares using the *ORFLS* program (Busing, Martin & Levy, 1962). The weight function was: $\sqrt{w}=16/F_o$, when $F_o\geq16$ and $\sqrt{w}=1$, when $F_o<16$. The final *R* value was 0·137 for 1249 reflexions. Hydrogen atoms were not included. The final atomic parameters are listed in Table 1.*

Discussion. Bond lengths and angles are shown in Fig. 1. Standard deviations are estimated to be 0·03 Å and 2° but somewhat larger values of about 0·05 Å and 3° are expected for the bonds involving C(24)~C(27). The palmitoyl group forms an all-*trans* zigzag chain as is usually found in fatty acids. The planarity of the chain is shown in Table 2. As indicated in Table 3, the conformation of the chloramphenicol (CM) moiety resembles that of bromamphenicol (BM; Dunitz, 1952). However, the terminal dichloro group takes a different orientation. The intramolecular hydrogen bond O(2)–H···O(3) suggested for BM is not found in CMP-β because O(2) is now an ester oxygen. Instead, O(3) participates in the intermolecular hydrogen bond O(3)^{i}–H···O(1)^{iv} of 2·71 Å, and also in a strong intramolecular bond with N(1)–H of 2·65 Å.

Projections of the crystal structure and an *ORTEP* (Johnson, 1965) drawing are shown in Figs. 2, 3 and 4. The long-chain palmitoyl groups are tilted at 45° to the molecular basal plane (010) in which the molecules are bound together along **c** by the hydrogen bond O(3)^{i}–H···O(1)^{iv} and also by the stacking of the *p*-nitrophenyl groups. The packing of the hydrocarbon chains is of the $O_\perp$ type. The approximate subcell

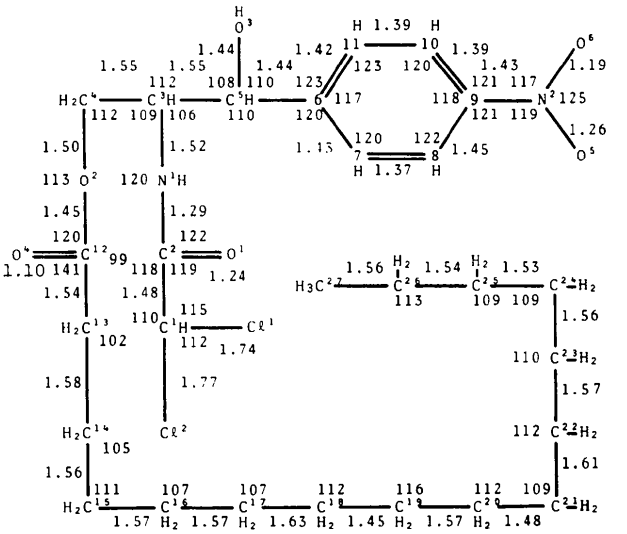

Fig. 1. Bond lengths (Å) and angles (°).

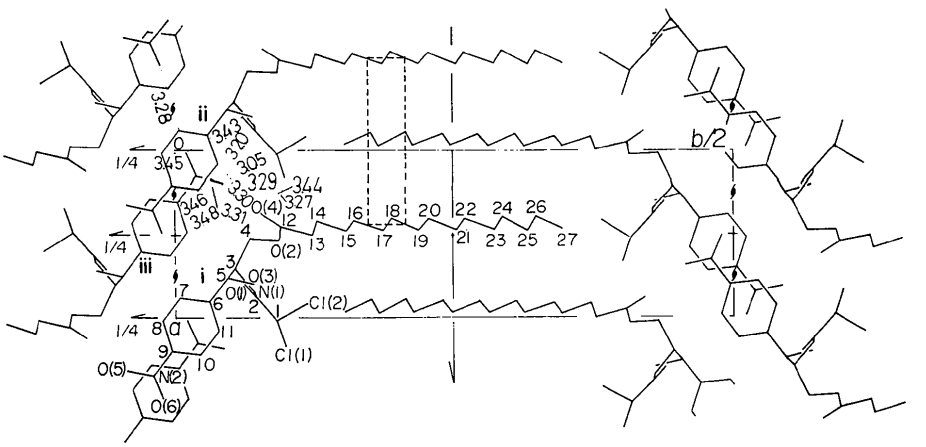

Fig. 2. Projection of the crystal structure along the *c* axis. Intermolecular short contacts less than 3·5 Å are shown by dotted lines. The molecules i at x,y,z; ii at $-1+x,y,z$; and iii at $\frac{1}{2}-x,-y,\frac{1}{2}+z$. The b_sc_s plane of a subcell defined for the hydrocarbon chains is shown by broken lines.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30571 (5pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

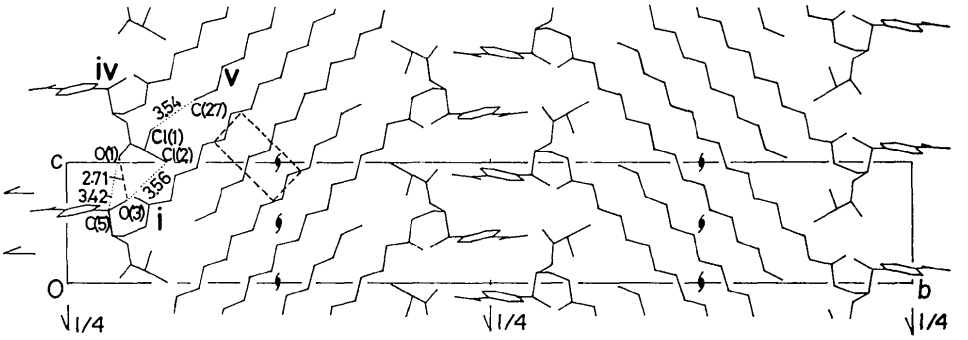

Fig. 3. Projection of the crystal structure along the *a* axis. The intermolecular hydrogen bond is shown by a broken line. The molecules i at x,y,z; iv at $x,y,1+z$; and v at $\frac{1}{2}+x,\frac{1}{2}-y,3-z$. The a_sc_s plane of a subcell is shown by broken lines.

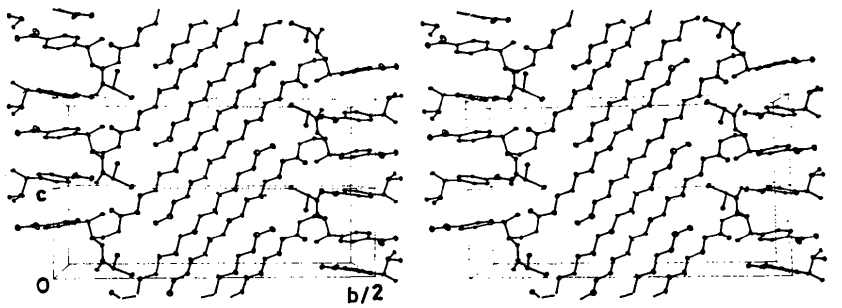

Fig. 4. Stereoscopic view along the *a* axis drawn by *ORTEP* (Johnson, 1965).

Table 2. *Planarity of the hydrocarbon chain*

The least-squares plane was calculated through all the atoms listed below.

Atom	Deviation	Atom	Deviation	Atom	Deviation
C(13)	0·04 Å	C(18)	−0·03 Å	C(23)	−0·04 Å
C(14)	0·07	C(19)	0·01	C(24)	−0·07
C(15)	−0·02	C(20)	−0·05	C(25)	0·07
C(16)	0·07	C(21)	−0·06	C(26)	0·01
C(17)	−0·07	C(22)	−0·02	C(27)	0·09

Table 3. *Comparison of some torsional angles found in CMP-β and bromamphenicol (BM)*

	CMP-β	BM
Cl(1)–C(1)–C(2)–O(1)	−163	−59
Cl(2)–C(1)–C(2)–O(1)	69	85
O(1)–C(2)–N(1)–C(3)	6	−1
C(2)–N(1)–C(3)–C(5)	155	108
N(1)–C(3)–C(5)–O(3)	47	69
N(1)–C(3)–C(4)–O(2)	−47	−72
O(3)–C(5)–C(6)–C(11)	−16	−30
C(10)–C(9)–N(2)–O(6)	−10	12

dimensions are $a_s=4{\cdot}95$, $b_s=7{\cdot}76$, $c_s=2{\cdot}52$ Å (see Figs. 2 and 3). It is interesting to see that the large tilt angle of the chain provides room for a contact of the terminal methyl group with the chlorine atoms. Furthermore, the chains situated at the corners of the subcells and those at the centres belong to different CM moieties each lying on the opposite side of the molecular layer. A similar arrangement of the chains, though with a slightly different type of chain packing, was also found in D-2-methyloctadecanoic acid (Abrahamsson, 1959), which also has a bulky group at the end of the chain. In CMP-β, the molecular layers shown in Fig. 4 are stacked along **b** to form a double layer. The direction of the tilt alternates in successive molecular layers giving rise to a herringbone arrangement of the molecules.

References

Abrahamsson, S. (1959). *Acta Cryst.* **12**, 304–309.

Aguiar, A. J., Krc, J. Jr, Kinkel, W. & Samyn, J. C. (1967). *J. Pharm. Sci.* **56**, 847–853.

Aguiar, A. J. & Zelmer, J. E. (1969). *J. Pharm. Sci.* **58**, 983–987.

Busing, W. R., Martin, K. O. & Levy, H. A. (1962). *ORFLS*. Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Dunitz, J. D. (1952). *J. Amer. Chem. Soc.* **74**, 995–999.

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

Tamura, C. & Kuwano, H. (1961). *J. Pharm. Soc. Japan*, **81**, 755–767.