

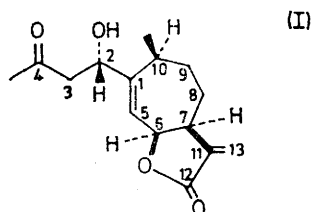
Crystal and Molecular Structure of Parthemollin {3,3a,4,5,6,8a-Hexahydro-7-(1-hydroxy-3-oxobutyl)-6-methyl-3-methylenecyclohepta[b]-furan-2-one}

By P. Sundararaman and Rognvald S. McEwen,*† Department of Chemistry, The Florida State University, Tallahassee, Florida 32306, U.S.A.

The crystal structure of the title compound (I) has been determined from three-dimensional X-ray diffractometer data by direct methods. Crystals are monoclinic, space group $P2_1$, with $Z = 2$ in a cell of dimensions: $a = 10.486(2)$, $b = 6.581(3)$, $c = 10.792(3)$ Å, $\beta = 111.79(2)^\circ$. The positions of all hydrogens other than those of methyl and hydroxy-groups were found and the structure refined by least squares to $R = 0.091$. The stereochemistry of the molecule has been established as having *cis*-fusion of the lactone ring, a result in contradiction to that suggested by an application of the Stöcklin-Waddell-Geissman rule of the lactone Cotton effect. Also Beecham's rule that the sign of the Cotton effect is determined by the chirality of the C:C:C:O chromophore is not valid in this case, the observed torsion angle being close to zero.

OPTICAL rotatory dispersion and circular dichroism have been useful in solving stereochemical problems in many areas of organic chemistry. The Cotton effect¹ is of particular importance and a number of empirical rules have been enunciated² which allow one to predict stereochemistry in specific systems from the sign of the effect. Exceptions to such rules have been noted.³

We report here on the break-down of a recently formulated rule of Stöcklin, Waddell, and Geissman,⁴ which relates the sign of the Cotton effect to the type of lactone ring closure in a series of naturally occurring sesquiterpene lactones. These compounds occur most commonly in five different skeletal forms, one being the xanthanolides. Chemical evidence has suggested the absolute configuration of the xanthanolide, parthemollin (I), but was unable to settle the type of fusion of the lactone ring.



The Stöcklin-Waddell-Geissman rule states that, regardless of structural type, *cis*-fused lactones closed at C(8) exhibit negative Cotton effects and that in *trans*-fused lactones closed at C(8), the Cotton effect is positive. The reverse is true for lactones closed to C(6). The strongly negative Cotton effect exhibited by parthemollin, comparable in magnitude to the effects of other xanthanolides, would therefore predict *trans*-fusion, a conclusion at variance with other evidence.⁵

In a discussion of lactone Cotton effects, Beecham⁶ suggested that in the case of α -methylene γ -lactones *trans*-fused to a six- or seven-membered ring, a positive

$n \rightarrow \pi^*$ Cotton effect is due to a right-handed chirality of the *cis*-oid C:C:C:O system. Left-handed chirality gives rise to a negative Cotton effect. McPhail and Sim,⁷ summarizing available crystallographic data on such lactones, pointed out that because of the relative rigidity of *trans*-fused lactones on six- or seven-membered rings it could be expected that the chirality of the C:C:C:O moiety would be determined by the position of the ring junction. In the case of the *cis*-fused lactones it is difficult to judge which chirality the chromophore would have on account of the flexibility of the lactone ring. From models it appears that the chirality can be made positive or negative by moving the atom opposite the ring junction bond, C(12) in the case of parthemollin, above or below the plane of the other lactone ring atoms without in any way disturbing the conformation of the cycloheptene ring. The reason for the signs of the C(α)-C(β)-C(γ)-O and C=C-C=O torsion angles to be paired as noted by Sim and McPhail for five *trans*- and two *cis*-lactones, is not obvious in the case of *cis*-lactones.

Because of the importance of Cotton-effect rules, and since no xanthanolides had hitherto been studied by X-ray diffraction, we undertook an investigation of parthemollin.

The results of the analysis establish that the lactone ring is *cis*-fused to the seven-membered ring. The positional and thermal parameters for the carbon and oxygen atoms are given in Table 1 and those for the hydrogen atoms located, in Table 2. Since the absolute configuration at several centres is known, the complete stereochemistry of parthemollin is as shown in (I). The views of the molecule in Figures 1 and 2 correspond to the known absolute configuration.

Stöcklin, Waddell, and Geissman noted that there are inconsistencies in the correlation of Cotton effect and ring-junction stereochemistry for *cis*-fused lactones and in the case of parthemollin also, the rule has failed to predict correctly the type of ring closure. Application of the

† Present address: British Aircraft Corporation, Dept. 821, Area 501, Filton House, Bristol BS99 7AR.

¹ P. Crabbe, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' 1965, Holden-Day, San Francisco.

² A. Moscovitz, E. Charney, U. Weiss, and H. Ziffer, *J. Amer. Chem. Soc.*, 1961, **83**, 4661.

³ D. R. Pollard and F. R. Ahmed, *Acta Cryst.*, 1971, **B27**, 1976.

⁴ W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, 1970, **26**, 2397.

⁵ W. Herz, S. B. Bhat, and A. L. Hall, *J. Org. Chem.*, 1970, **35**, 1100.

⁶ A. F. Beecham, *Tetrahedron*, 1972, **28**, 5543.

⁷ A. T. McPhail and G. A. Sim, *Tetrahedron*, 1973, **29**, 1751.

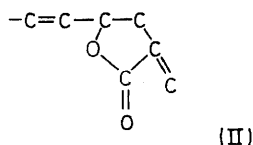
TABLE 1

Positional ($\times 10^4$) and thermal ($\times 10^4$) parameters * for carbon and oxygen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	6633(05)	2065(12)	4432(06)	292(29)	329(36)	389(32)	-58(22)	137(22)	58(22)
C(2)	6201(06)	2459(13)	2931(05)	367(30)	448(43)	341(30)	-132(25)	98(22)	-54(26)
C(3)	7459(06)	3011(15)	2602(06)	425(34)	594(51)	358(31)	-135(31)	155(25)	-07(29)
C(4)	7093(08)	3566(19)	1140(08)	600(45)	951(78)	454(41)	-195(46)	253(35)	34(42)
C(5)	6392(05)	3405(12)	5211(05)	281(27)	294(35)	349(30)	35(20)	96(21)	94(21)
C(6)	6867(05)	3200(12)	6692(05)	291(27)	370(37)	371(31)	15(23)	136(21)	60(23)
C(7)	8446(05)	2927(13)	7465(05)	333(30)	444(42)	376(32)	-40(25)	102(23)	-127(26)
C(8)	9278(06)	2501(17)	6576(07)	298(30)	755(59)	474(37)	-52(31)	148(25)	05(37)
C(9)	8947(07)	0519(16)	5814(08)	392(36)	681(61)	587(44)	-268(36)	147(30)	-23(37)
C(10)	7399(06)	0100(14)	5040(06)	411(34)	456(43)	467(36)	-80(28)	193(27)	-90(29)
C(11)	8844(06)	4863(15)	8209(05)	371(33)	598(48)	325(32)	-36(30)	113(24)	89(29)
C(12)	7608(06)	6162(15)	7961(06)	454(36)	520(47)	324(33)	-65(29)	152(26)	-21(28)
C(13)	10080(08)	5500(17)	8987(08)	464(38)	635(64)	626(45)	-147(39)	115(34)	-214(41)
C(14)	7229(08)	-1640(17)	4093(08)	623(47)	551(56)	725(52)	42(39)	307(40)	-02(41)
C(15)	6177(12)	2067(25)	0140(09)	1021(73)	1163(107)	499(47)	-306(75)	315(48)	-329(57)
O(1)	5266(05)	4063(11)	2491(04)	438(27)	473(34)	359(26)	-10(21)	63(19)	58(19)
O(2)	7527(05)	7796(14)	8346(05)	537(33)	862(55)	489(32)	-20(32)	148(24)	-170(32)
O(3)	6509(04)	5048(00)	7214(04)	344(25)	614(38)	458(28)	04(22)	149(19)	-151(24)
O(4)	7574(09)	5018(20)	0843(07)	1237(65)	1463(94)	701(45)	-553(65)	386(44)	286(53)

* In the form: $\exp[-2\pi^2(h^2a^*U_{11} + k^2b^*U_{22} + l^2c^*U_{33} + 2hka^*b^*U_{12} + 2hla^*c^*U_{13} + 2klb^*c^*U_{23})]$.

rule to lactones of the type shown in partial formula (II) has already been commented on.^{8,9}



Bond lengths and angles are given in Tables 3 and 4. No abnormal inter- or intra-molecular atomic contacts

TABLE 2

Positional ($\times 10^3$) and thermal ($\times 10^2$) * parameters for hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	U
H(2)	578(05)	127(09)	238(05)	1.94 (0.27)
H(3A)	807(07)	181(13)	293(07)	4.00 (1.82)
H(3B)	783(05)	415(10)	323(05)	1.80 (1.29)
H(5)	586(04)	453(08)	486(04)	0.26 (0.95)
H(6)	642(04)	200(08)	688(04)	0.66 (1.03)
H(7)	857(06)	173(12)	806(06)	2.74 (1.62)
H(8A)	913(05)	369(10)	593(05)	1.97 (1.34)
H(8B)	1025(08)	283(16)	718(08)	5.61 (2.21)
H(9A)	924(06)	-096(12)	646(06)	3.05 (1.64)
H(9B)	946(08)	027(16)	510(08)	5.54 (2.39)
H(10)	700(10)	-059(21)	574(10)	8.40 (3.22)
H(13A)	1076(10)	456(19)	906(09)	6.44 (3.04)
H(13B)	1022(07)	687(15)	925(08)	4.29 (2.04)

* Temperature factors are of the form: $\exp[-8\pi^2U(\sin\theta)^2/\lambda^2]$.

were calculated. Important torsional angles are listed in Table 5.

The γ -lactone ring together with its exocyclic methylene group are very flattened, the sum of the internal torsional angles being 39° . This value is much smaller than it is in other similar compounds, *e.g.* 67° in pseudovalin bromoacetate,¹⁰ and 116° in axivalin.¹¹ The deviation of the atoms from the best plane through all of them are:

⁸ W. Herz and S. V. Bhat, *J. Org. Chem.*, 1972, **37**, 906.

⁹ W. Herz and S. V. Bhat, *Phytochem.*, 1973, **12**, 1737.

¹⁰ R. Gitany, G. D. Anderson, and R. S. McEwen, *Acta Cryst.*, 1974, **B30**, 1900.

C(6) -0.07, C(7) 0.01, C(11) 0.01, C(13) 0.01, C(12) -0.01, O(2) -0.04, and O(3) 0.09 [a negative sign indicates the atom is on the upper side of the ring as shown

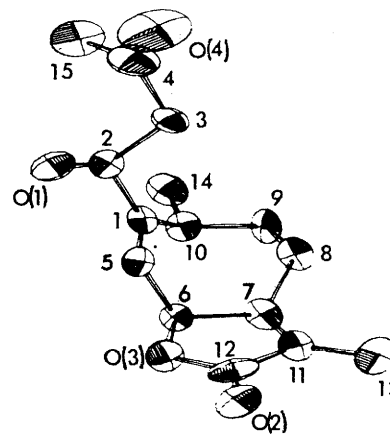
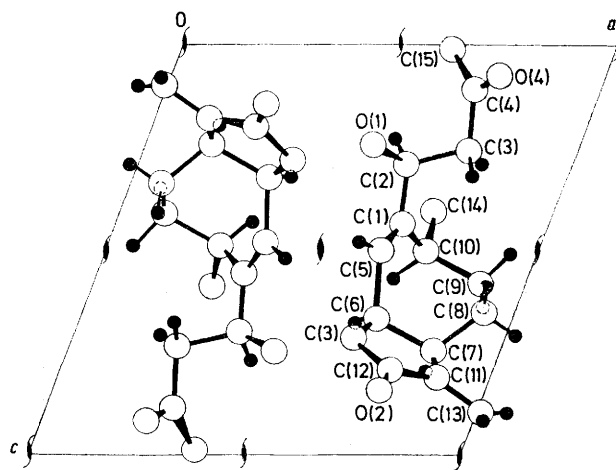


FIGURE 1 ORTEP plot of the molecular structure

FIGURE 2 Projection of the structure down the b axis

¹¹ G. D. Anderson, R. S. McEwen, and W. Herz, *Acta Cryst.*, 1973, **B29**, 2783.

in (I)]. The angle C(13)=C(11)-C(12)=O(2) is 1° , $<1\sigma$ from zero. Since the Cotton effect is negative, Beecham's suggestion that it is controlled by the chirality of the C:C:C:O chromophore is not borne out in this case. The O(3)-C(6)-C(7)-C(11) angle is -8° , so here also the ring junction and chromophore angles are not correlated as they are in *trans*-fused lactones. An examination of the

TABLE 3

Bond lengths (Å), with estimated standard deviations in parentheses

C(1)-C(2)	1.533(08)	C(6)-O(3)	1.447(08)
C(1)-C(5)	1.306(10)	C(7)-C(8)	1.563(07)
C(1)-C(10)	1.536(11)	C(7)-C(11)	1.481(12)
C(2)-C(3)	1.532(10)	C(8)-C(9)	1.512(14)
C(2)-O(1)	1.398(10)	C(9)-C(10)	1.549(09)
C(3)-C(4)	1.523(11)	C(10)-C(14)	1.500(14)
C(4)-O(4)	1.179(17)	C(11)-C(12)	1.491(11)
C(4)-C(15)	1.514(16)	C(11)-C(13)	1.324(10)
C(5)-C(6)	1.493(08)	C(12)-O(3)	1.351(08)
C(6)-C(7)	1.563(07)	C(12)-O(2)	1.167(13)

TABLE 4

Bond angles (deg.) with estimated standard deviations in parentheses

C(2)-C(1)-C(5)	120.9(7)	C(6)-C(7)-C(8)	114.9(5)
C(2)-C(1)-C(10)	119.8(8)	C(6)-C(7)-C(11)	102.7(6)
C(5)-C(1)-C(10)	119.3(6)	C(11)-C(7)-C(8)	112.5(7)
C(3)-C(2)-C(1)	110.1(4)	C(7)-C(8)-C(9)	115.2(7)
C(3)-C(2)-O(1)	107.3(7)	C(8)-C(9)-C(10)	115.5(7)
O(1)-C(2)-C(1)	112.4(6)	C(1)-C(10)-C(9)	110.9(7)
C(4)-C(3)-C(2)	112.9(5)	C(14)-C(10)-C(9)	109.8(7)
C(15)-C(4)-C(3)	115.6(9)	C(14)-C(10)-C(1)	116.1(6)
O(4)-C(4)-C(3)	120.5(8)	C(7)-C(11)-C(12)	110.1(5)
O(4)-C(4)-C(15)	123.8(9)	C(7)-C(11)-C(13)	128.9(8)
C(1)-C(5)-C(6)	124.1(6)	C(12)-C(11)-C(13)	120.9(9)
C(5)-C(6)-C(7)	116.6(5)	C(11)-C(12)-O(3)	106.7(7)
C(5)-C(6)-O(3)	108.0(6)	C(11)-C(12)-O(2)	129.6(7)
O(3)-C(6)-C(7)	105.4(5)	O(3)-C(12)-O(2)	123.6(7)

TABLE 5

Torsion angles * (deg.)

	ϕ		ϕ
C(10)-C(1)-C(5)-C(6)	3	O(3)-C(6)-C(7)-C(11)	-8
C(1)-C(5)-C(6)-C(7)	57	C(6)-C(7)-C(11)-C(12)	2
C(5)-C(6)-C(7)-C(8)	-11	C(7)-C(11)-C(12)-O(3)	5
C(6)-C(7)-C(8)-C(9)	-64	C(11)-C(12)-O(3)-C(6)	-11
C(7)-C(8)-C(9)-C(10)	49	C(12)-O(3)-C(6)-C(7)	12
C(8)-C(9)-C(10)-C(1)	37	C(13)-C(11)-C(12)-O(2)	1
C(9)-C(10)-C(1)-C(5)	-74		

* The torsional angle ϕ (1)-(2)-(3)-(4) denotes the angle between a plane defined by atoms (1)-(2)-(3) and a plane defined by atoms (2)-(3)-(4). The angle is positive if the bond in front has to be turned clockwise in order to eclipse the rear bond.

TABLE 6

Sign of the Cotton effect in some *cis*-fused sesquiterpene γ -lactones

Compound	Cotton effect	Ring junc.	Ring junc. torsion \angle	Chromophore torsion \angle
Parthemollin	-	(6)-(7)	-8	1
Pseudoivalin	-	(7)-(8)	20	7
bromoacetate				
Axivalin	+	(6)-(7)	34	12
Bromohelenalin	-	(7)-(8)	38	17

C=C=C=O angles in other *cis*-fused γ -lactones for which the c.d. is known, reveals that in three cases, a positive torsion angle corresponds to a negative Cotton effect,

¹² Mazhar-ul-Haque and C. N. Caughlin, *J. Chem. Soc. (B)*, 1967, 355.

while in one case a positive angle corresponds to a positive effect. Relevant data are summarized in Table 6. In bromomexicanin-E,¹² bromohelenalin,¹³ pseudoivalin bromoacetate,¹⁰ and axivalin,¹¹ the ring junction and chromophore torsion angles have the same sign, while in parthemollin they have opposite signs. It would seem that in *cis*-fused lactones, the ring-junction torsion angle does not control the chromophore angle which may then be determined by crystal forces. In solution, the chirality may be differently determined by solvent interaction thereby eliminating a correlation between the sign of the effect and angle as observed in the solid state. If the solution and solid-state torsion angles do have the same small value, an alternative possibility is that there is no direct relationship between chromophore chirality and Cotton-effect sign, but that in the rigid *trans*-fused lactones the position of ring closure determines both. The sign of the Cotton effect may be determined by the overall chirality of the lactone ring system.¹⁴

The cycloheptene ring adopts a boat conformation in parthemollin, and this appears to be the only conformation in which interactions between the C(10) methyl and other parts of the molecule are minimized. The presence of the fused lactone ring does not appear to impose this conformation on the seven-membered ring, for a twist-boat form would result in only a moderately large O(3)-C(6)-C(7)-C(11) angle. However, a very severe C(10)(Me)-C(1) side-chain interaction would develop. It can be seen from the torsion angles (Table 5) that the boat is slightly distorted from C_s symmetry, for C(5)-C(6)-C(7)-C(8) and C(8)-C(9)-C(10)-C(1) are of different magnitudes. A perfect C_s boat would have C(6), C(7), C(9), and C(10) all in a plane. In parthemollin, C(10) lies 0.49 Å out of the plane of C(6), C(7), and C(9). Finally C(8) at the 'prow' is displaced to the starboard quarter.

EXPERIMENTAL

Crystal Data.— $C_{15}H_{20}O_4$, $M = 264.3$. Monoclinic, $a = 10.486(2)$, $b = 6.581(3)$, $c = 10.792(3)$ Å, $\beta = 111.79(2)^\circ$, $U = 691.5$ Å³, $D_c = 1.27$, $Z = 2$, $D_m = 1.28$ (by flotation). $F(000) 284$. Space group $P2_1(C_2)$. Mo- K_α radiation, $\lambda = 0.71069$ Å; $\mu(\text{Mo}-K_\alpha) = 0.983$ cm⁻¹.

Crystallographic Measurements.—A small crystal was examined by Weissenberg photography before data collection. It was then mounted with its longest dimension, which was coincident with the b axis, approximately parallel to the ϕ shaft of a Hilger and Watts, four-circle automatic diffractometer. A least-squares fit of the observed angles of twelve high-order reflections gave refined cell parameters and an orientation matrix. Data were collected to $2\theta = 60^\circ$ by use of Zr-filtered, Mo radiation, the 2θ - ω -scan technique, a scintillation counter, and pulse-height discrimination. 4321 Measurements were made, including three standard reflections monitored throughout the experiment. Data were corrected for minor fluctuations of the standard intensities and equivalent reflections averaged to give 1907 independent structure factors after application of standard corrections.

¹³ Mazhar-ul-Haque and C. N. Caughlin, *J. Chem. Soc. (B)*, 1969, 956.

¹⁴ G. A. Sim, personal communication.

Structure Analysis.—All computations were performed on a CDC 6600 computer using local modifications of the 'X-Ray '72' system of programmes¹⁵ and a plotting programme.¹⁶ Atomic form factors were taken from ref. 17.

The structure was solved by an application of the symbolic-addition and tangent-refinement methods. The origin-defining reflections [7,0,4; 8,1,1; and 5,0,1] were assigned phases in accordance with the usual rules, and three further reflections were then assigned symbolic phases: $\bar{1}2,0,10$; $\bar{1},1,2$; and $\bar{1},4,7$. $\Sigma 2$ Relationships¹⁵ were then generated, and by application of TANGEN reflection, 8,7,1 was chosen as enantiomer-defining. The agreement factor, after reiterative application of the tangent refinement formula, was 0.15, with 264 phases determined. These 264 phases gave an *E* map which revealed the positions of the 19 heavy atoms of the structure. A structure-factor calculation for carbon atoms at these positions gave *R* 0.335.

Refinement.—Two cycles of full-matrix least-squares refinement minimizing $\Sigma(F_o - kF_c)^2$ using individual isotropic temperature factors and unit weights lead to *R* 0.235.

* Observed and calculated structure factors are published in Supplementary Publication No. SUP 21174 (11 pp., 1 microfiche). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

¹⁵ J. M. Stewart, G. J. Kruger, M. L. Ammon, C. Dickenson, and S. R. Hall, 1972, Technical Report TR 192, Computer Science Centre, University of Maryland.

Replacement of carbon atoms with oxygen at the appropriate positions reduced *R* to 0.197.

At this point observed reflections were redefined as having $I > 3\sigma(I)$ and the following weighting scheme was used: $w = X \cdot Y$ where $X = 1$ if $F_o < 8$ and $X = 8/F_o$ otherwise, and $Y = 1$ if $\sin \theta > 0.35$ and $Y = \sin \theta / 0.35$ otherwise. For $F_o < 3\sigma$, these weights were reduced by a factor of 10. Several extinction-affected reflections were assigned zero weight. Anisotropic refinement of the 19 heavy atoms brought *R* to 0.132 over the 1881 observed reflections. Of the 20 hydrogen atoms, 13 not belonging to hydroxy- and methyl-groups were readily located from a difference map and included in the model. The final values of *R* and *R'* were 0.091 and 0.12.*

We thank Professor W. Herz for suggesting the problem and supplying the crystals of parthemollin, the F.S.U. computing centre for allocating state funds to this project, and the U.S. Public Health Service through the National Cancer Institute and the Research Corporation for partial financial support of this work.

[4/1569 Received, 29th July, 1974]

¹⁶ C. K. Johnson, 1970, ORTEP: A Fortran Thermal-Ellipsoid Plot Programme for Crystal Structure Illustrations, Report ORNL 3794, Oak Ridge National Laboratory.

¹⁷ 'International Tables for X-Ray Crystallography,' vol. III, 1968, Kynoch Press, Birmingham.