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Absolute Crystal Structure of $C_9H_{12}O_4$ Determined by Three-Beam Scattering

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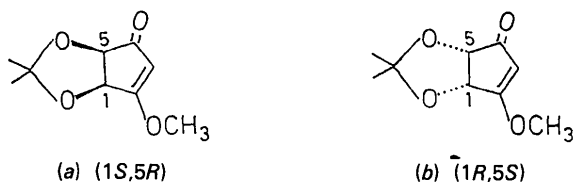
Abstract

(1R,5S)-8-Methoxy-3,3-dimethyl-2,4-dioxabicyclo-[3.3.0]oct-7-en-6-one, $C_9H_{12}O_4$, $M_r = 184 \cdot 19$, orthorhombic, $P2_12_12_1$, $a = 18 \cdot 296$ (2), $b = 7 \cdot 8292$ (7), $c = 6 \cdot 5741$ (7) Å, $V = 941 \cdot 70$ Å^3, $Z = 4$, $D_x = 1 \cdot 299$ g cm^{-3}, λ(Mo $K\alpha$) $= 0 \cdot 70926$ Å, $\mu = 0 \cdot 958$ cm^{-1}, $F(000) = 392$, room temperature, final $R(F) = 0 \cdot 064$ for 999 reflections. The absolute structure was determined by measurements of intensity changes in three-beam positions caused by multiple-scattering effects. A definite result was obtained in spite of the poor quality of the crystal; the title compound has a (1R,5S) rather than a (1S,5R) configuration as originally proposed.

Introduction

According to Bestmann & Moenius (1986) the title compound has a (1S,5R) absolute configuration. Additional chemical investigations, however, gave rise to doubts with respect to this correlation. As the title compound is the basis for the synthesis of a series of

natural compounds it seemed to be necessary to decide between the configurations (*a*) and (*b*) by the determination of the absolute structure.

(*a*) (1*S*,5*R*)   (*b*) (1*R*,5*S*)

Experimental

The synthesis of the title compound was performed in five steps starting with natural (*R,R*)-tartaric acid. The procedure reported by Bestmann & Moenius (1986) was used, except that the rings were produced by an intramolecular Wittig reaction using an autoclave with inert gas pressure as reported by Roth (1988).

All measurements were performed on a rebuilt PW 1100 instrument. Crystal dimensions $0.40 \times 0.40 \times 0.15$ mm; ω–2θ scan; modified Lehmann–Larsen profile analysis; lattice parameters derived from 60 reflections with $13.4 < \theta < 19.8°$; absorption correction by using a modified version of *CAMEL JOCKEY* (Flack, 1975), transmission factors 0.98–1.06; intensities collected for $-21 \le h \le 21$, $-9 \le k \le 9$, $-7 \le l \le 7$; $\theta_{max} = 25°$; eight standard reflections repeated after 200 reflections; decrease of intensity by decomposition of the crystal under X-ray radiation to 76% of the initial intensity, correction for decay applied; 6628 reflections measured; 999 unique reflections after merging; no unobserved reflections omitted; 12 F values with negative intensities were set to zero; R_{int} based on F is 0.028.

The structure was solved by direct methods and refined by full-matrix least squares based on F; weights derived from experimental standard deviations $w = 1/\sigma^2(F)$ and $\sigma = \text{max.}(0.01F, \sigma_{exp})$. In the later stages of refinement anisotropic temperature parameters were
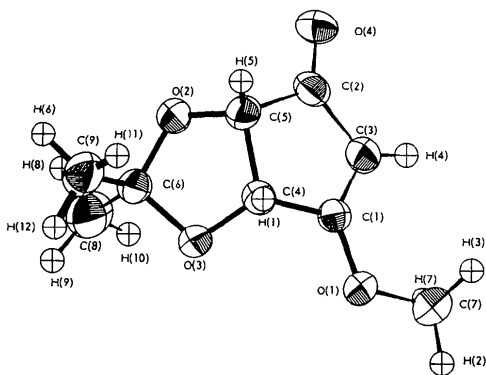
used for all non-H atoms. All H atoms could be located on a difference Fourier map. Least-squares refinement, however, gave unsatisfactory distances and angles for four H atoms in the methyl groups C(8) and C(9) (Fig. 1). Thus their coordinates were calculated and held fixed for the final refinement using a common isotropic temperature factor for all H atoms. The resulting
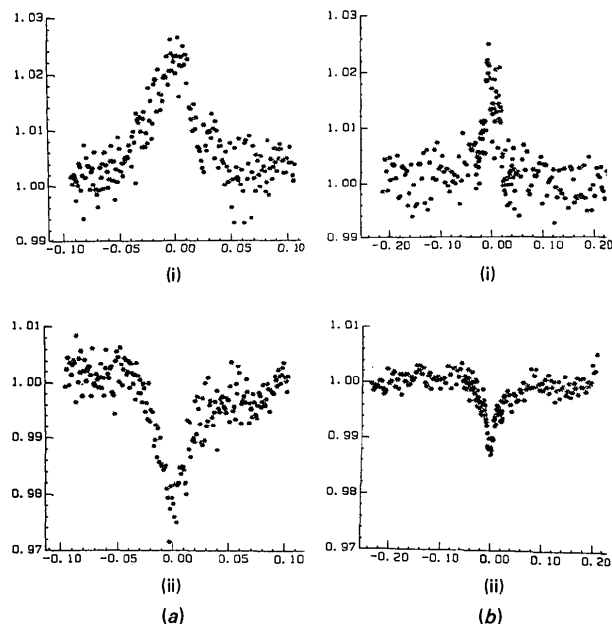
Table 1. *Fractional coordinates and U_{eq} or U_{iso} values (Å^2)*

	Occupation	x	y	z	U
O(1)	1·000 (–)	0·3294 (1)	0·5581 (3)	0·5582 (4)	0·0633
O(2)	1·000 (–)	0·4265 (1)	1·0412 (3)	0·7660 (5)	0·0694
O(3)	1·000 (–)	0·3304 (1)	0·8642 (3)	0·8187 (5)	0·0654
O(4)	1·000 (–)	0·5317 (1)	0·9204 (4)	0·4576 (5)	0·0852
C(1)	1·000 (–)	0·3844 (2)	0·6669 (4)	0·5777 (5)	0·0499
C(2)	1·000 (–)	0·4825 (2)	0·8423 (5)	0·5351 (7)	0·0623
C(3)	1·000 (–)	0·4368 (2)	0·7120 (5)	0·4486 (7)	0·0587
C(4)	1·000 (–)	0·3910 (2)	0·7536 (5)	0·7798 (6)	0·0556
C(5)	1·000 (–)	0·4562 (2)	0·8737 (5)	0·7512 (7)	0·0586
C(6)	1·000 (–)	0·3596 (2)	1·0271 (5)	0·8732 (6)	0·0577
C(7)	1·000 (–)	0·3229 (3)	0·4736 (7)	0·3645 (9)	0·0861
C(8)	1·000 (–)	0·3095 (3)	1·1644 (7)	0·803 (1)	0·1131
C(9)	1·000 (–)	0·3724 (3)	1·0368 (8)	1·0982 (8)	0·0970
H(1)	1·000 (–)	0·404 (1)	0·670 (4)	0·902 (4)	0·080 (5)
H(2)	1·000 (–)	0·280 (2)	0·389 (4)	0·396 (4)	0·080 (5)
H(3)	1·000 (–)	0·369 (2)	0·406 (4)	0·352 (4)	0·080 (5)
H(4)	1·000 (–)	0·442 (1)	0·670 (4)	0·328 (5)	0·080 (5)
H(5)	1·000 (–)	0·492 (2)	0·847 (4)	0·845 (5)	0·080 (5)
H(6)	1·000 (–)	0·395 (1)	1·146 (4)	1·136 (4)	0·080 (5)
H(7)	1·000 (–)	0·314 (1)	0·566 (4)	0·252 (4)	0·080 (5)
H(8)	1·000 (–)	0·339 (1)	1·267 (4)	0·806 (4)	0·080 (5)
H(9)	1·000 (–)	0·264 (–)	1·170 (–)	0·898 (–)	0·080 (5)
H(10)	1·000 (–)	0·293 (–)	1·139 (–)	0·653 (–)	0·080 (5)
H(11)	1·000 (–)	0·407 (–)	0·937 (–)	1·143 (–)	0·080 (5)
H(12)	1·000 (–)	0·322 (–)	1·026 (–)	1·174 (–)	0·080 (5)

Fig. 1. Projection of the molecule with 35% probability thermal ellipsoids for non-H atoms.

Fig. 2. ψ-scan profiles around three-beam positions. The two-beam intensity is scaled to unity. $\psi = 0$ fixes the three-beam position; for $\psi < 0$ (h',k',l') is inside the Ewald sphere. (*a*) Triplet pair: (2,–1,0), (–3,1,1), (1,0,–1) (i) and (–2,1,0), (3,–1,–1), (–1,0,1) (ii). (*b*) Triplet pair: (0,–2,0), (2,1,1), (–2,1,–1) (i) and (0,2,0), (–2,–1,–1), (2,–1,1) (ii).

Table 2. Bond distances (Å) and angles (°)

O(1)–C(1)	1·325 (3)	C(7)--O(1)–C(1)	116·32 (8)
–C(7)	1·440 (3)		
O(2)–C(6)	1·416 (3)	C(5)–O(2)–C(6)	106·95 (5)
–C(5)	1·422 (2)		
O(3)–C(6)	1·428 (2)	C(4)–O(3)–C(6)	107·18 (5)
–C(4)	1·429 (3)		
C(1)–O(1)	1·325 (3)	C(3)–C(1)–O(1)	131·1 (2)
–C(3)	1·328 (3)	C(4)–C(1)–O(1)	116·03 (8)
–C(4)	1·496 (3)	C(4)–C(1)–C(3)	112·84 (7)
C(2)–O(4)	1·202 (3)	C(3)–C(2)–O(4)	129·0 (2)
–C(3)	1·436 (3)	C(5)–C(2)–O(4)	123·4 (1)
–C(5)	1·520 (3)	C(5)–C(2)–C(3)	107·50 (6)
C(3)–H(4)	0·86 (2)	C(1)–C(3)–H(4)	124·5 (7)
–C(1)	1·328 (3)	C(2)–C(3)–H(4)	124·7 (7)
–C(2)	1·436 (3)	C(2)–C(3)–C(1)	110·85 (7)
C(4)–H(1)	1·06 (1)	O(3)–C(4)–H(1)	114·2 (4)
–O(3)	1·429 (3)	C(1)–C(4)–H(1)	114·1 (4)
–C(1)	1·496 (3)	C(1)–C(4)–O(3)	111·79 (6)
–C(5)	1·530 (3)	C(5)–C(4)–H(1)	107·3 (2)
		C(5)–C(4)–O(3)	104·72 (4)
		C(5)–C(4)–C(1)	103·47 (4)
C(5)–H(5)	0·93 (1)	O(2)–C(5)–H(5)	115·7 (4)
–O(2)	1·422 (2)	C(2)–C(5)–H(5)	111·0 (4)
–C(2)	1·520 (3)	C(2)–C(5)–O(2)	109·49 (6)
–C(4)	1·530 (3)	C(4)–C(5)–H(5)	109·6 (3)
		C(4)–C(5)–O(2)	105·14 (4)
		C(4)–C(5)–C(2)	105·20 (5)
C(6)–O(2)	1·416 (3)	O(3)–C(6)–O(2)	105·55 (4)
–O(3)	1·428 (2)	C(8)–C(6)–O(2)	108·76 (6)
–C(8)	1·486 (4)	C(8)–C(6)–O(3)	109·68 (6)
–C(9)	1·500 (3)	C(9)–C(6)–O(2)	110·61 (7)
		C(9)–C(6)–O(3)	110·55 (6)
		C(9)–C(6)–C(8)	111·49 (8)
C(7)–H(3)	1·00 (1)	H(2)–C(7)–H(3)	108·7 (4)
–H(2)	1·05 (1)	H(7)–C(7)–H(3)	115·9 (6)
–H(7)	1·05 (1)	H(7)–C(7)–H(2)	117·2 (6)
–O(1)	1·440 (3)	O(1)–C(7)–H(3)	104·3 (2)
		O(1)–C(7)–H(2)	100·2 (1)
		O(1)–C(7)–H(7)	108·6 (3)
C(8)–H(8)	0·97 (1)	H(9)–C(8)–H(8)	113·4 (4)
–H(9)	1·044 (4)	H(10)–C(8)–H(8)	110·1 (3)
–H(10)	1·052 (4)	H(10)–C(8)–H(9)	109·7 (1)
–C(6)	1·486 (4)	C(6)–C(8)–H(8)	104·3 (2)
		C(6)–C(8)–H(9)	109·72 (9)
		C(6)–C(8)–H(10)	109·42 (9)
C(9)–H(6)	0·99 (2)	H(11)–C(9)–H(6)	108·8 (3)
–H(11)	1·046 (3)	H(12)–C(9)–H(6)	108·5 (3)
–H(12)	1·051 (3)	H(12)–C(9)–H(11)	109·65 (9)
–C(6)	1·500 (3)	C(6)–C(9)–H(6)	111·1 (4)
		C(6)–C(9)–H(11)	109·48 (8)
		C(6)–C(9)–H(12)	109·22 (8)

Table 3. Phases of the triplet invariants

(a) Reflections for triplets

h	k	l	$|F_{obs}|$	φ (°)
2	1	0	53·1	180·0
0	2	0	40·9	0·0
1	0	1	72·6	90·0
2	1	1	61·7	146·3
3	1	1	93·0	−17·7

(b) List of triplets referring to Fig. 2

	h	k	l	φ (°)	h	k	l	φ (°)
$-h_{basic}$	2	−1	0	0·0	−2	1	0	0·0
k_{moved}	−3	1	1	17·7	3	−1	−1	−17·7
$(h-k)_{coupling}$	1	0	−1	−90·0	−1	0	1	90·0
				$\Phi = -72.3°$				$\Phi = 72.3°$

	h	k	l	φ (°)	h	k	l	φ (°)
$-h_{basic}$	0	−2	0	0·0	0	2	0	0·0
k_{moved}	2	1	1	146·3	−2	−1	−1	−146·3
$(h-k)_{coupling}$	−2	1	−1	146·3	2	−1	1	−146·3
				$\Phi = -67.4°$				$\Phi = 67.4°$

(c) Additional triplets measured

	h	k	l	φ (°)	h	k	l	φ (°)
$-h_{basic}$	−2	−1	−1	−146·3	2	1	1	146·3
k_{moved}	0	2	0	0·0	0	−2	0	0·0
$(h-k)_{coupling}$	2	−1	1	−146·3	−2	1	−1	146·3
				$\Phi = 67.4°$				$\Phi = -67.4°$

	h	k	l	φ (°)	h	k	l	φ (°)
$-h_{basic}$	2	1	0	180·0	−2	−1	0	180·0
k_{moved}	−3	−1	−1	17·7	3	1	1	−17·7
$(h-k)_{coupling}$	1	0	1	90·0	−1	0	−1	−90·0
				$\Phi = -72.3°$				$\Phi = 72.3°$

coordinates and U_{eq} values are given in Table 1.* The final R values are $R = 0.064$, $wR = 0.063$, $S = 3.8$, maximal shift-to-e.s.d. ratio 0·02. Maximal and minimal electron density residuals are $\Delta\rho_{max} = 0.30$ and $\Delta\rho_{min} = -0.35\,e\,\text{Å}^{-3}$. Extinction corrections were applied according to Zachariasen (1968); the maximal extinction factor was 1·008; form factors from *International Tables for X-ray Crystallography* (1974). All computations were performed on an Atari Mega ST2 computer using the next release of the program system *ATARI CRYSTAN*88 (Burzlaff & Rothammel, 1988).

Determination of the absolute structure

The absolute structure was determined by measurements of suitable triplet phase invariants. As shown

theoretically by Hümmer & Billy (1986) it is possible to obtain information on triplet phase invariants by three-beam scattering experiments based on ψ-scan techniques. The experimental proof was reported by Bondza, Hümmer & Weckert (1986) and Hümmer, Weckert & Bondza (1989). For the experiment a six-circle diffractometer was used (Burzlaff, Bondza, Hümmer & Weckert, 1989) that allows the mechanical alignment of a scattering vector to a hardware ψ axis with a high angular resolution of 0·001° for ψ rotations.

The basic scattering vector (h,k,l) is brought into reflection position, *i.e.* the points (0,0,0) and (h,k,l) of the reciprocal lattice lie on the Ewald sphere; the intensity related to (h,k,l) is recorded during the scan. If a third vector (h',k',l') moves to the Ewald sphere an additional wave field is excited which interacts with that due to (h,k,l) *via* the difference or coupling vector $(h-h',\ k-k',\ l-l')$. The interaction leads to systematic changes in the recorded intensity of (h,k,l). The changes are uniquely related to the triplet invariant $\Phi = \varphi(-h,-k,-l) + \varphi(h',k',l') + \varphi(h-h',k-k',l-l')$ and the ratio of the related structure-factor moduli. The case $\Phi \simeq +\pi/2$ decreases, the case of $\Phi \simeq -\pi/2$ increases the intensity of (h,k,l) if the ratio of the related moduli is approximately 1:2:2. As enantiomorphic structures differ in the sign of suitable triplet invariants the structures can be distinguished experimentally especially if Φ is close to $\pm\pi/2$. Because the variation of the intensity is also influenced by the phase-independent effects of *Aufhellung* and *Umweganregung* governed by the ratio of the moduli it is reasonable to

compare the pairs of centrosymmetrically related invariants $\Phi[(-h,-k,-l)$, (h',k',l'), $(h-h',k-k',l-l')]$ and $\Phi[(h,k,l)$, $(-h',-k',-l')$, $(h'-h,k'-k,l'-l)]$. Figs. 2(a) and 2(b) show the experimental results for two pairs of triplets, which are in good agreement with the phases of the triplet invariants calculated on the basis of the coordinates listed in Table 1 (cf. Table 3). These results were confirmed for two different crystals and several pairs of triplets by experiments with synchrotron radiation and rotating-anode equipment using two different six-circle instruments; no discrepancies were observed. Thus the determination of the absolute structure is clear cut in spite of the poor quality of the crystals and their decay under X-ray irradiation.

Discussion

There are no unusual distances and angles in the molecule (see Table 2). The chiral atoms are C(4) and C(5); the distribution of their neighbours as given in Fig. 1 defines the absolute structure (b) i.e. (1R,5S).

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Structural Studies on the Biosides of *Digitalis lanata*: Bisdigitoxosides of Digitoxigenin, Gitoxigenin and Digoxigenin

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Abstract

The crystal structures and conformations of bisdigitoxosides of digitoxigenin (I), gitoxigenin (II) and digoxigenin (III and IV) have been determined using single-crystal X-ray crystallographic techniques. Crystals of (I), (II) and (IV) were grown from ethyl acetate solutions of the glycosides while (III) was grown from a solution of the digitoxoside in ethanol. As in other cardiac glycosides the ring junctions A–B and C–D are cis. The D ring in these structures shows different conformations while the A, B and C rings remain conformationally similar. Although digitoxigenin bisdigitoxoside and gitoxigenin bisdigitoxoside differ from each other in the absence and presence of a hydroxyl group at C(16) of the D ring, these two biosides crystallize in the space group P2$_1$2$_1$2$_1$ and are isomorphous. The presence of the hydroxyl group at

C(16) does not affect the orientation of the lactone ring and the conformation of the molecule. Digoxigenin bisdigitoxoside crystallizes in two different crystal systems with four molecules of water in the orthorhombic form and one molecule of ethyl acetate in the triclinic form. In both forms the hydroxyl at C(3') of the first sugar forms a hydrogen bond with the ring oxygen of the second sugar. This has also been observed in the trioside digoxin. The torsion angle C(13)–C(17)–C(20)–C(22) in the two forms differs by 7°. Crystal data at $T = 298$ K, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å: (I) C$_{35}$H$_{54}$O$_{10}$.C$_4$H$_8$O$_2$, $M_r = 722.8$, orthorhombic, P2$_1$2$_1$2$_1$, $a = 11.447$ (1), $b = 14.303$ (1), $c = 23.982$ (3) Å, $V = 3926$ Å^3, $Z = 4$, $D_x = 1.223$ g cm^{-3}, $\mu = 6.97$ cm^{-1}, $F(000) = 1568$, $R = 0.071$ for 3006 observed reflections; (II) C$_{35}$H$_{54}$O$_{11}$.C$_4$H$_8$O$_2$, $M_r = 738.8$, orthorhombic, P2$_1$2$_1$2$_1$, $a = 11.351$ (2), $b = 14.392$ (3), $c = 23.738$ (6) Å, $V =$