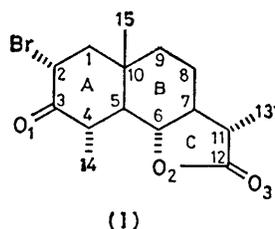


Crystal and Molecular Structure of 2 α -Bromo- α -tetrahydrosantonin

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X-Ray analysis of 2 α -bromo- α -tetrahydrosantonin, in addition to confirming the stereochemistry of α -tetrahydrosantonin as envisaged by earlier workers, shows that the *trans*-fused rings A and B adopt the chair conformation and the *trans*-fused γ -lactone ring adopts an envelope conformation with C(7) being the out-of-plane atom. The crystals are monoclinic, space group $P2_1$, with $a = 8.099(5)$, $b = 7.248(6)$, $c = 13.317(4)$ Å, $\beta = 102.74^\circ$, $Z = 2$. The structure was solved by the heavy atom method and refined by full matrix least squares calculations to an R value of 0.086 using 1 008 independent photographically recorded reflections.

WEIGHAUS and VON QETTINGEN,¹ Wedking and Beniers,² and Simonsen³ recorded the preparation of two of the four possible tetrahydrosantonins, the so-called α -isomer, m.p. 155–156°, and the β -isomer, m.p. 106°. Yanagita and Tahara⁴ described the α -isomer as having a *cis*-A/B ring fusion which was subsequently revised by Tahara⁵ to *trans*. Cocker and McMurry⁶ supported this and showed 4-methyl group to be axial in the α -orientation and 11-Me to be β -oriented. Yanagita and Tahara⁴ reported that treatment of α - and γ -tetrahydrosantonin with bromine gave exclusively the 2-bromo-compounds but similar treatment of three decalins was always accompanied by rearrangement.^{7,8} In view of these observations the possibility of 4-bromination in α -tetrahydrosantonin was ruled out by Yamakawa⁹ who fixed bromine in the 2-position as an α -oriented equatorial substituent, *trans* to the 10-methyl group. In confirmation of this, our X-ray analysis establishes the structure of 2 α -bromo- α -tetrahydrosantonin (I).



EXPERIMENTAL

Crystal Data.—2 α -Bromo- α -tetrahydrosantonin, C₁₅H₂₁BrO₃, m.p. 145°. $M = 329.2$. Monoclinic, space group $P2_1(C_2^2)$, $a = 8.099(5)$, $b = 7.248(6)$, $c = 13.317(4)$ Å, $\beta = 102.74(6)^\circ$, $U = 762.6$ Å³, $Z = 2$, $D_c = 1.433$, $D_m = 1.432$ g cm⁻³, $\mu_{Cu-K\alpha} = 40.58$ cm⁻¹.

Crystallographic Measurements.—Well defined crystals were obtained by controlled evaporation from methanol. Rotation, oscillation, and Weissenberg photographs were taken using Cu- $K\alpha$ radiation (λ 1.5418 Å). After long exposure to X-rays (ca. 100 h), the crystal turned light yellow but there was no noticeable change in the relative intensities. The crystal used had the dimensions $0.3 \times 0.2 \times 0.3$ mm³. Cell dimensions were calculated by the least-squares method involving high angle spots. Intensities of reflections in the reciprocal lattice nets $h0l$ — $h5l$ were estimated visually from equi-inclination Weissenberg

photographs and corrected for Lorentz, polarisation, and rotation¹⁰ effects in the usual way but no allowance was made for absorption. The intensities were placed on an approximate absolute scale by the Wilson method,¹¹ taking into consideration cross level reflections from the $0kl$ level. In all, 1 008 independent reflections were employed.

Structure Analysis.—The x and z co-ordinates of the heavy atom were initially derived from a three-dimensional Patterson synthesis and a Harker section. Fixing of the origin by taking the y co-ordinate of bromine as 0.25 resulted in pseudo-symmetry and superimposition of mirror images on the initial three-dimensional electron density distribution. On the basis of the bromine position alone the R value was 0.42 and the inclusion of all carbon and oxygen positions, picked up from the first and second Fourier synthesis, reduced R to 0.28. The atomic co-ordinates were fixed by Booth's numerical interpolation method¹² and refined by three rounds of Fourier synthesis to R 0.216. During this the gradual shift of the O(1) atom towards its correct position away from the pseudo-mirror plane at $y = 1/4$ was observed.

Subsequent improvements of the positional and isotropic thermal parameters, obtained from five cycles of full matrix least-squares refinement using program XFLS, reduced R to 0.103. Three further rounds of refinement with anisotropic thermal parameters reduced R to a final value of 0.086. Unit weights (w) were given for the initial five cycles and $\sqrt{w} = |F_o|/19.16$ for $|F_o| < 19.16$ and $\sqrt{w} = 19.16/|F_o|$ for $|F_o| > 19.16$ for the last three cycles. Finally a difference Fourier was calculated but this failed to distinguish the hydrogen peaks from the background ripples. The atomic scattering factors from ref. 13 were used.

RESULTS AND DISCUSSION

The composite final molecule viewed down the b axis together with the numbering scheme is shown in Figure 1. Figure 2 illustrates the packing of the molecules as viewed down the b axis. The fractional atomic co-ordinates and the estimated standard deviations are listed in Table 1. The interatomic distances and bond angles along with the estimated standard deviations are presented in Tables 2 and 3, respectively. The mean planes calculated through different parts of the molecular framework and displacements of different atoms from these are given in Table 4. Important intramolecular non-bonded distances, anisotropic temperature factors, and the observed and calculated structure

TABLE 1

2 α -Bromo- α -tetrahydrosantonin. Atomic co-ordinates as fractions of cell edge, with estimated standard deviations in parentheses ($\times 10^4$)

	<i>x</i>	<i>y</i>	<i>z</i>
Br	0.174 1(6)	0.250 0(0)	0.056 0(4)
O(1)	0.501 0(8)	0.206 7(9)	0.986 1(6)
O(2)	0.516 9(7)	0.405 7(8)	0.588 9(5)
O(3)	0.622 1(7)	0.408 0(8)	0.446 3(5)
C(1)	0.118 0(10)	0.339 2(12)	0.835 7(5)
C(2)	0.249 2(8)	0.369 5(10)	0.937 8(5)
C(3)	0.412 6(7)	0.301 4(9)	0.916 1(5)
C(4)	0.470 1(9)	0.398 1(12)	0.827 3(6)
C(5)	0.334 3(9)	0.366 3(9)	0.730 6(6)
C(6)	0.366 7(8)	0.451 5(10)	0.630 4(6)
C(7)	0.237 6(8)	0.395 0(10)	0.533 3(6)
C(8)	0.078 1(9)	0.493 2(10)	0.548 3(6)
C(9)	0.037 5(10)	0.416 7(11)	0.642 2(5)
C(10)	0.168 2(7)	0.447 3(9)	0.747 4(6)
C(11)	0.320 8(7)	0.472 1(10)	0.449 5(6)
C(12)	0.506 7(8)	0.433 3(10)	0.488 9(5)
C(13)	0.269 8(9)	0.371 9(12)	0.345 7(6)
C(14)	0.638 0(8)	0.301 1(12)	0.820 5(6)
C(15)	0.168 3(11)	0.658 5(11)	0.764 4(7)

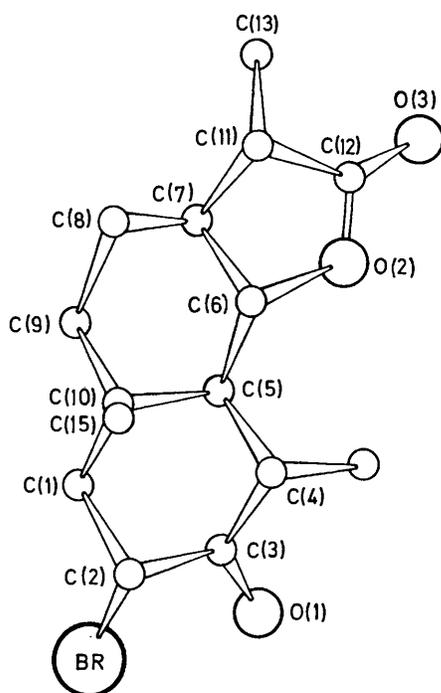


FIGURE 1 The atomic arrangement in the molecule seen in projection along the *b* axis

TABLE 2

2 α -Bromo- α -tetrahydrosantonin. Bond lengths (\AA) with standard deviation in parentheses

Bond	Length	Bond	Length
Br-C(2)	2.006(7)	C(5)-C(6)	1.545(11)
O(1)-C(3)	1.251(10)	C(5)-C(10)	1.530(9)
O(2)-C(6)	1.480(9)	C(6)-C(7)	1.529(11)
O(2)-C(12)	1.331(11)	C(7)-C(8)	1.526(10)
O(3)-C(12)	1.210(9)	C(7)-C(11)	1.532(10)
C(1)-C(2)	1.546(10)	C(8)-C(9)	1.531(11)
C(1)-C(10)	1.541(10)	C(9)-C(10)	1.526(10)
C(2)-C(3)	1.499(9)	C(10)-C(15)	1.548(10)
C(3)-C(4)	1.534(10)	C(11)-C(12)	1.508(9)
C(4)-C(5)	1.516(11)	C(11)-C(13)	1.536(12)
C(4)-C(14)	1.552(10)		

factors are in Supplementary Publications No. SUP 22775 (8 pp.).*

This analysis follows the numbering scheme adopted for the parent compound santonin by White and Sim.¹⁴ It establishes the compound as a *trans*-fused decalin (as predicted by Tahara⁵ and Cocker and McMurphy⁶) with

TABLE 3

2 α -Bromo- α -tetrahydrosantonin. Valency angles ($^\circ$) with the standard deviations in parentheses

Bonds	Angle	Bonds	Angle
C(12)-O(2)-C(6)	117.7(6)	C(6)-C(7)-C(8)	101.9(7)
C(10)-C(1)-C(2)	110.7(7)	C(11)-C(7)-C(6)	100.9(5)
C(1)-C(2)-Br	111.1(6)	C(11)-C(7)-C(8)	116.5(6)
C(3)-C(2)-Br	116.3(5)	C(7)-C(8)-C(9)	107.0(6)
C(1)-C(2)-C(3)	104.4(6)	C(8)-C(9)-C(10)	117.5(6)
C(2)-C(3)-O(1)	115.3(9)	C(1)-C(10)-C(5)	107.8(6)
C(4)-C(3)-O(1)	126.9(6)	C(1)-C(10)-C(9)	110.2(5)
C(2)-C(3)-C(4)	115.4(8)	C(1)-C(10)-C(15)	112.6(7)
C(3)-C(4)-C(5)	107.4(6)	C(5)-C(10)-C(9)	106.2(6)
C(14)-C(4)-C(3)	104.9(6)	C(5)-C(10)-C(15)	115.4(6)
C(14)-C(4)-C(5)	111.3(6)	C(9)-C(10)-C(15)	104.4(6)
C(4)-C(5)-C(6)	116.4(6)	C(7)-C(11)-C(12)	104.2(8)
C(10)-C(5)-C(4)	108.3(7)	C(7)-C(11)-C(13)	114.2(8)
C(5)-C(6)-O(2)	122.9(8)	O(3)-C(12)-O(2)	124.2(7)
C(7)-C(6)-O(2)	96.2(6)	C(11)-C(12)-O(2)	102.3(6)
C(5)-C(6)-C(7)	114.1(6)	C(11)-C(12)-O(3)	132.9(6)
C(10)-C(5)-C(6)	107.2(6)	C(12)-C(11)-C(13)	106.0(6)

rings A and B adopting distorted chair conformations. In the cyclohexanone ring A C(2), C(3), C(5), and C(10) are closely coplanar with negligible deviations and C(1) and C(4) are displaced by -0.75 and 0.73 \AA respectively towards opposite sides of plane I (Table 4). The sp^2 carbon C(3) deviates from plane II only by 0.67 \AA compared with -0.76 \AA for C(10) indicating the dis-

TABLE 4

Equations of the mean planes through various sets of atoms and deviations (\AA) of atoms from the planes. Atoms not included in the derivation of a plane are italicised.

Plane I $-0.384\ 03X - 0.906\ 06Y - 0.177\ 68Z - 4.3255 = 0$

C(2) -0.02 , C(3) 0.02 , C(5) -0.02 , C(10) 0.02 , C(1) -0.75 , C(4) 0.73 , C(15) 1.42 , O(1) -0.24 , Br -2.08

Plane II $-0.149\ 35X + 0.985\ 52Y - 0.080\ 33Z + 1.7724 = 0$

C(1) -0.002 , C(2) 0.002 , C(5) -0.002 , C(4) 0.002 , C(10) -0.767 , C(3) 0.67 , Br 0.23 , C(14) 0.89 , C(15) -2.27

Plane III $-0.4363X - 0.8974Y - 0.0654Z - 3.2137 = 0$

C(5) 0.03 , C(10) -0.033 , C(7) -0.033 , C(8) 0.033 , C(6) 0.75 , C(9) -0.65 , C(15) 1.33 , C(11) 0.79

Plane IV $0.0534X - 0.9185Y - 0.3917Z - 6.1389 = 0$

C(5) -0.013 , C(6) 0.014 , C(8) -0.014 , C(9) 0.014 , C(10) 0.686 , C(7) -0.814 , O(2) -0.57

Plane V $-0.1051X + 0.9784Y - 0.1778Z + 1.580 = 0$

C(6) -0.048 , C(7) 0.048 , C(9) -0.048 , C(10) 0.047 , C(5) 0.729 , C(8) -0.753 , C(11) -0.595 , O(2) 0.322

Plane VI $-0.1844X - 0.9729Y - 0.1389Z - 4.3881 = 0$

C(11) -0.012 , C(12) 0.041 , O(2) -0.012 , O(3) -0.018 , C(6) 0.139 , C(7) -0.574 , C(13) -0.926

tortion of ring A. Similarly in the cyclohexane ring B C(6) and C(9) are on opposite sides of plane III by 0.75 and -0.65 \AA , respectively. Planes I and III are closely parallel, the dihedral angle between them being 7° . The opposite deviations of C(1) and C(6) and of C(4) and C(9)

* For details of Supplementary Publications see Notice to Authors No. 7, in *J.C.S. Perkin II*, 1979, Index issue.

with respect to the planes I and III show that rings A and B are *trans*-fused. C(15) is in the axial position and β -oriented whereas the bromine attached to C(2) is in an α -oriented equatorial position, *trans* to the angular 10-methyl group. The 4-methyl group is in an α -oriented pseudo-equatorial position (see Table 4).

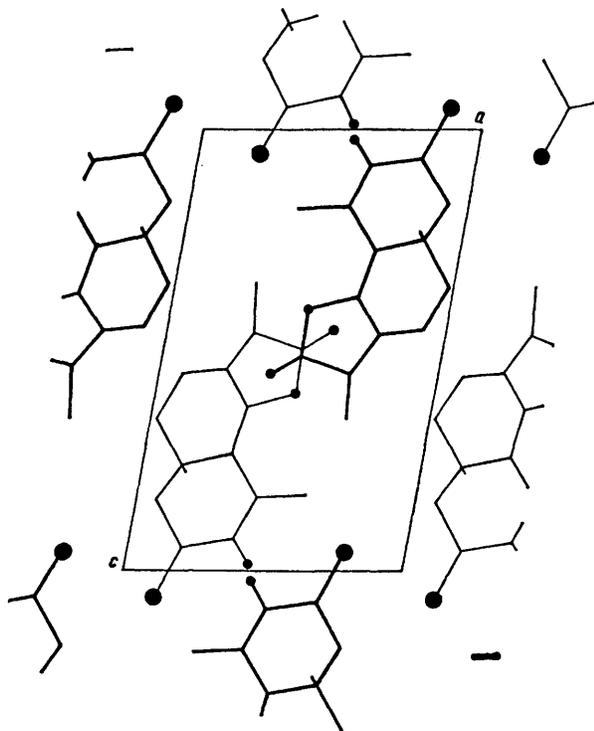


FIGURE 2 The crystal structure viewed in projection along the *b* axis

The γ -lactone ring is *trans*-fused to ring B at C(6) and C(7) and approaches the envelope form with C(7) and C(6) deviating by -0.57 and 0.14 Å respectively from the mean plane through C(11), C(12), O(2), and O(3). The trend is similar to that in α -santonin,¹⁵ β -santonin,¹⁶ fluoguinolide,¹⁷ and a number of other γ -lactones.

The bond lengths are in good agreement with those reported in the literature. The $C_{sp^3}-C_{sp^3}$ bond lengths vary from 1.516 to 1.551 Å with a mean value of 1.535 ± 0.010 Å. The average $C_{sp^3}-C_{sp^3}$ single bond is 1.51 ± 0.01 Å and the mean $C_{sp^3}-O$, $C_{sp^2}-O$, and $C=O$ bond lengths are 1.48 , 1.33 , and 1.23 Å, respectively. The $C_{sp^3}-Br$ distance of 2.006 Å is slightly longer than those observed normally.¹⁸ The C(12)-O(2) bond of 1.33 Å adjacent to carbonyl group is shorter than the C(6)-O(2) bond of 1.48 Å as in tamqulipin,¹⁹ germacranolide,²⁰ and santonins.¹⁴⁻¹⁶

The angle C(7)-C(6)-O(2) in the γ -lactone ring at 96.2° is considerably smaller than the reported values.^{19,20} This angle is 99.0° in 2β -bromo- γ -tetrahydrosantonin.²¹ The mean valency angles in ring A, ring B, and the γ -lactone ring are 109 , 109.3 , and 104.0° , respectively. The distortion caused by the fusion of the distorted γ -lactone ring to ring B results in a larger spread of the tetrahedral angle values, $102.0-117.5^\circ$.

The exocyclic 11-methyl group which reverses the stabilities in santonins ($\alpha > \beta$) and 6-*epi*-santonins ($\beta < \alpha$)^{14,22} is in an α -oriented equatorial position (plane IV, Table 4). The non-bonded intramolecular contact of C(13) with O(3) at 2.88 Å is smaller than that in α -santonin (3.02 Å) and in 6-*epi*- β -santonin (3.00 Å). The corresponding values for the less stable β -santonin and 6-*epi*- α -santonin are 3.17 and 3.14 Å, respectively. In santonins and 6-*epi*-santonins White and Sim²³ have shown that the van der Waals steric considerations are not prominent factors in deciding the stabilities and an exocyclic group at C(11) in the quasi-equatorial orientation is subject to smaller strain than in the quasi-axial orientation. The present findings are in line with these arguments. The tendency of C(13) to eclipse O(3) in the γ -lactone together with the greater flexibility of the cyclohexane rings in 2- α -bromo- α -tetrahydrosantonin appears to result in a shorter contact between C(13) and O(3) and a decrease in the angle C(12)-C(11)-C(13) to 106° from the value of 111° in 2-bromo- α -santonin.

Intermolecular contacts are generally normal. Some intermolecular contacts involving O(1) are among the shortest. These are O(1)-C'(2) 3.18 Å, O(1)-C'(3) 3.23 , and O(1)-C'(4) 3.31 Å. Shorter intermolecular contacts of O(3) to C'(11) and O(3) to C'(6) at 3.44 and 3.47 Å are similar to those observed in 2-bromo- α -santonin. The molecules are stacked in layers parallel to the (010) plane as seen in Figure 2.

We thank Drs. A. M. Shaligram and V. S. Johrapur for the sample of 2- α -bromo- α -tetrahydrosantonin and Mr. J. K. Suri for help in computations which were performed on an EC-1030 computer, I.I.T., Bombay. One of us (S. V. L. N.) is also indebted to I.I.T., Bombay, for a Fellowship.

[9/1639 Received, 16th October, 1979]

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