Studies on the Chlorinated α-Santonins. IV.[1] Chlorination of α-Santonin and Stereochemistry Therein

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Addition of chlorine to the double bond of α-santonin derivatives such as santonin chlorohydrin (4) santonin α-epoxide (5), and 5-chloro-4-methoxysantonin (6) produced new chloro-santonins (13, 14, 16, respectively). So far, only *trans* addition of chlorine to the 1,2-double bond of santonin has been known, but from the configuration of these products, it was clear that *cis* addition had occurred. 'Santonin dichloride' (2), and 2-chlorosantonin (3), were chloro-methoxylated and chloro-hydroxylated to produce tetrasubstituted compounds (9 and 10), and trisubstituted compounds (11 and 12), respectively. Their structure and configuration were determined by interrelating them to known santonin derivatives (2, 3, 4, 5, and 6) and by X-ray analysis of 13.

Keywords α-santonin; chlorination; X-ray analysis; polychloro santonin; *cis* addition; stereochemistry

It is well known that the chlorination of α-santonin (**1**) in chloroform produces only santonin dichloride (**2**), but we found that santonin tetrachloride (**7**) was produced by adding acetic acid to the reaction system.[2] To develop our finding, we carried out the chlorination of the 1,2-double bond of compounds **4**, **5** and **6** in chloroform–acetic acid to give **16**, **14**, and **13**, respectively. The structure of the product (**13**) from **6** was elucidated by X-ray analysis to be 1α,2α,5β-trichloro-1,2-dihydro-4α-methoxysantonin.

In the nuclear magnetic resonance (NMR) spectra, coupling constants between the 1- and 2-hydrogen atoms of **14** and **16** are 2 and 6 Hz, respectively, being similar to that of **13** (6 Hz). This fact shows that **14** and **16** have the same configuration as **13** at the positions 1 and 2. Up to the present, only *trans* addition to the 1,2-double bond of α-santonin has been known, but we have found that *cis* addition occurs in this case.

To obtain the isomers of **13** and **16**, chloro-methoxylation and chloro-hydroxylation of **2** were carried out to get **10** and **9** respectively. To clarify the configurations of these new compounds, chloro-hydroxylation and chloro-methoxylation of **3** were also carried out to get **11** and **12**, respectively. The configurations of these polychloro compounds were determined by relating them to **2**, **4**, **5**, and **6**, whose structures are already known, or to the key compound (**13**) whose structure we have now revealed.

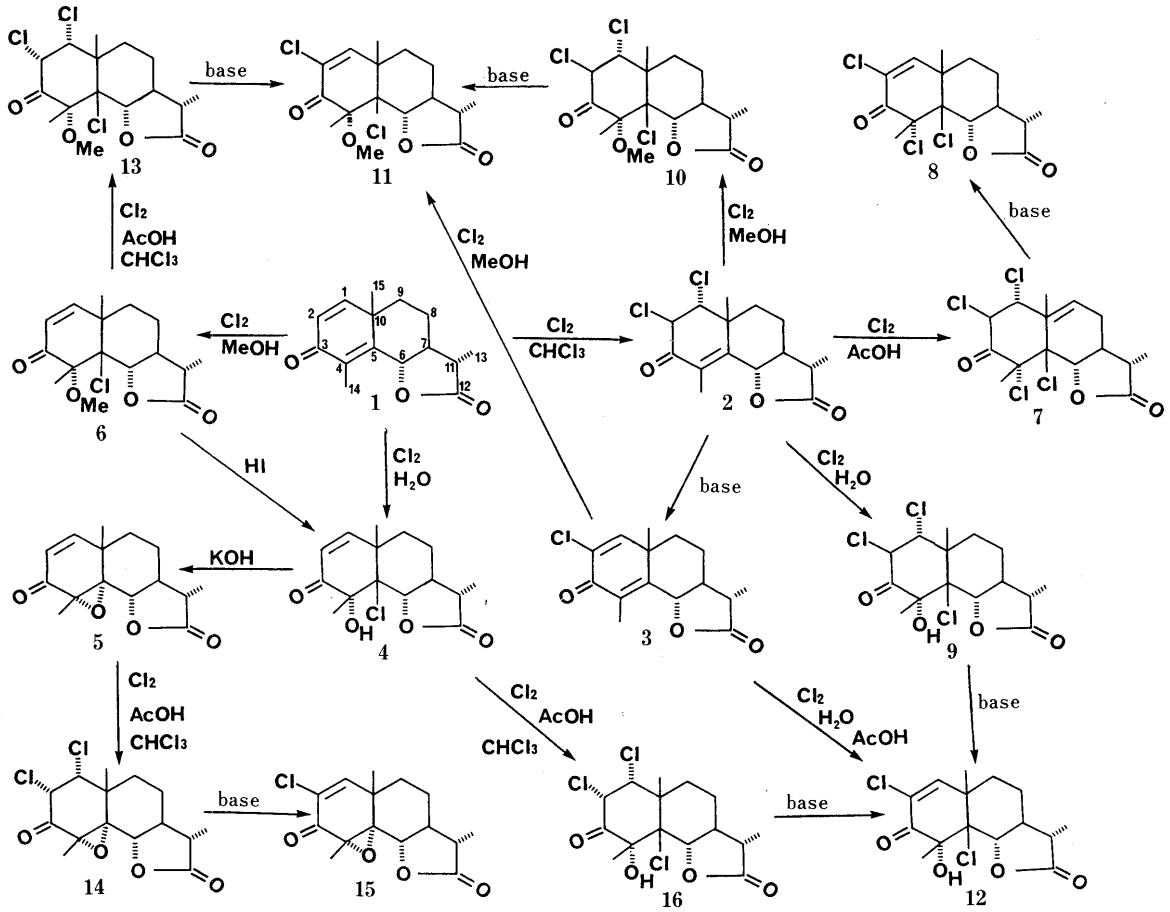

Chart 1

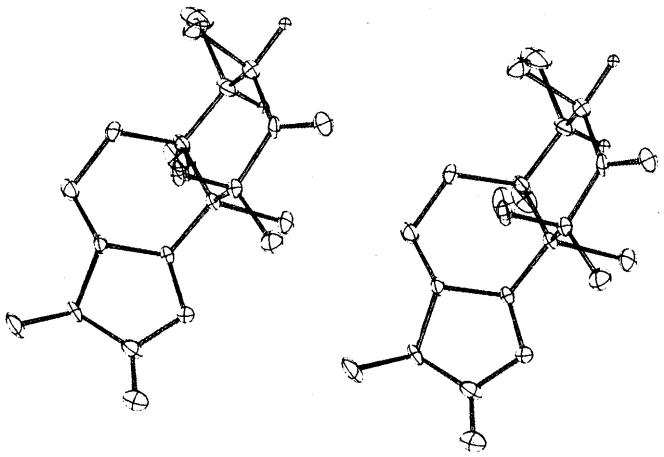

Fig. 1. ORTEP Drawing of the Molecule of **13**

All hydrogen atoms, except for two hydrogen atoms attached to C1 and C2, are excluded for clarity. (Thermal ellipsoids are drawn at the 50% probability level).

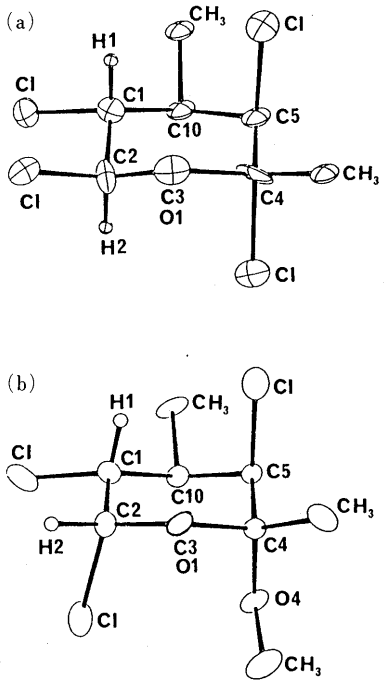

Fig. 2. a) Perspective Drawing of Ring A of 1α,2β,4α,5β-Tetrachlorosantonin (**7**), Viewed along the Carbonyl Group
b) Perspective Drawing of the A Ring of 1α,2α,5β-Trichloro-4α-methoxysantonin (**13**), Viewed along the Carbonyl Group

Reaction of 'santonin dichloride' (**2**) with chlorine in chloroform–acetic acid affords the tetrachloride (**7**), and this compound could be dehydrochlorinated with base to give the corresponding 2,4,5-trichlorosantonin (**8**).[2] Chlorination of 5β-chloro-4α-methoxysantonin (**6**) in chloroform–acetic acid gave **13**. The presence of a saturated carbonyl group in **13** was proved by carbonyl absorption at 1730 cm^{-1} ($CHCl_3$) in the infrared (IR) spectrum and ultraviolet (UV) absorptions in $CHCl_3$ at 252, and 328 nm (ε 1700 and 40). This product was dehydrochlorinated with base to produce 2,5β-dichloro-4α-methoxysantonin (**11**). Compound **11** was also prepared by the action of chlorine on a methanolic solution of 2-chlorosantonin (**3**).

The dichlorohydroxy compound (**12**) can be prepared by addition of the elements of hypochlorous acid to **3**, using chlorine in aqueous acetic acid, and by addition of chlorine (in chloroform–acetic acid) to **4**. In the latter reaction, addition of chlorine to the 1,2-double bond is accompanied by dehydrochlorination of a part of compound **16**. Santonin α-epoxide (**5**) was chlorinated in a mixture of chloroform–acetic acid to yield 1,2-dichloro-4,5-epoxysantonin (**14**), which was easily dehydrochlorinated to produce 2-chloro-4,5-epoxysantonin (**15**). The reaction of 'santonin dichloride' (**2**) with chlorine in aqueous acetic acid as a solvent, affords 1,2-dihydro-4-hydroxy-1,2,5-trichlorosantonin (**9**), which with base affords the corresponding dichlorohydroxy compound (**12**). Carbonyl absorption at 1755 cm^{-1} ($CHCl_3$) in the IR spectrum, and UV absorption in EtOH at 248 nm (ε 1400) indicate the presence of a saturated carbonyl group in **9**. In MeOH as a solvent, the dichloro compound (**2**) reacts with chlorine to afford the methoxy-trichloro compound (**10**), which underwent dehydrochlorination with base to afford **11**. Compound **10** also has a saturated carbonyl group as judged from the absorption at 1753 cm^{-1} (KBr) in the IR, and the UV absorption in $CHCl_3$ at 252 and 306 nm (ε 400 and 60).

As **11** is formed from **13** and also from **10**, the configurations at C-4 and C-5 must be the same in compounds **10**, **11**, and **13**. As **10** is formed from **2**, the configurations of the 1- and 2-chlorines in **10** must be α and β, respectively. These facts undoubtedly indicate that compound **10** is a stereoisomer of **13**. Compound **12** is derived from **4** *via* **16** and from **2** *via* **9**. It follows that as the configurations at the 4- and 5-carbons are known in **4**, the configurations at the same center in **16**, **12**, and **9** are 5β-chloro-4α-hydroxy, too. The configuration at the 1- and 2-centres in **9** must be the same as in **2**, *i.e.* 1α, 2β-chloro. Compound **16** is an isomer of **9**, and must have 1α, 2α-chlorines as in **13**. This is supported by the NMR spectrum of **16** which shows the same coupling constant (J 6 Hz) for the 1- and 2-protons, as is found in **13**. This indicates that in **13** and **16**, the 1,2-equatorial-axial hydrogen dihedral angle is approximately 30°, which is slightly different from the result of X-ray structure determination of **13** (Table III). The 1,2-diaxial hydrogen coupling constants for **2**, **9**, and **10** are all 12 Hz, indicating that these hydrogens in each case show a dihedral angle of approximately 180°. Compound **14** is easily decomposed, but the corresponding coupling constant of 2 Hz indicated that compound **14** also must have 1α,2α-chlorines, and in this case, the dihedral angle between the 1- and 2-hydrogens was approximately 60°.

X-Ray analysis of **13** shows that ring A has a deformed chair form like that of the tetrachloride (**7**)[2] (Figs. 1 and 2). The comparison of its torsion angle values with those in the tetrachloride indicates some degree of flattening at the part of the ring where Cl(2) is attached (torsion angle values of 45 and −48 against 55 and −58°) (Table III), and closing at C(5) where β-oriented chlorine atom is attached (−51 and 49 against 43 and 44°). An equatorial chlorine atom in compound **7** and an axial one in **13** at C(2) may explain these differences.

The different modes of addition of chlorine to santonin deserve some comment. With chlorine in Water, or MeOH, santonin gives products (**4**, **6**) which are derived from attack of chlorine on the more electron-rich 4,5-double bond. In

these polar and hydrogen bonding solvents, chlorine will be more solvated, and hence a 'softer' reagent, which would attack the 'softer' double bond. In chloroform, chlorine will not be as solvated, and hence a 'harder' reagent. In this case, it will attack the 'harder' 1,2-double bond. Attack on the 4,5-double bond takes place from the β-side, presumably because steric interactions involving the lactone ring inhibit attack from the α-side. This is in contrast with the hydrogenation of santonin, which leads to products derived mainly from α-addition to the 4,5-bond. In this latter case, the lactone ring may assist absorption of the α-face on the catalyst surface, by itself being absorbed on the surface.

Experimental

General Methods Unless otherwise stated the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage apparatus and are uncorrected. IR spectra were taken in $CHCl_3$ or KBr with a Hitachi 260-10 spectrometer and are given in cm^{-1}. UV spectra were recorded in EtOH with a Hitachi 200-10 spectrophotometer. ^{1}H-NMR (100 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL FX-100 spectrometer. High-resolution mass spectra (MS) were recorded on a JEOL JMS-D300 mass spectrometer. For column chromatography, silica gel (Wako-gel C-200) was used.

1α,2β-Dichlorosantonin (2) **2** was prepared from **1** according to Wedekind and Koch.[3] **2**: Colorless plates. mp 169—171 °C (dec.), [lit.,[3] 173 °C (dec.)]. IR and NMR spectral data were identical with those reported.

2-Chlorosantonin (3) **3** was prepared from **2** according to Wedekind and Koch. **3**: Colorless plates mp 221—223 °C (dec.), [lit.,[3] 224 °C (dec.)]. IR and NMR spectral data were identical with those reported.

Santoninchlorohydrin (4) (a) Preparation of **4** from Santonin (**1**): This was prepared after Wedekind and Tettweiler.[4] **4**: Colorless plates. mp 235—236 °C (dec.), [lit.,[4] 235—236 °C (dec.)]. IR and NMR spectral data were identical with those reported.

(b) Preparation from 5β-Chloro-4α-methoxysantonin (**6**): This was prepared as described in the literature.[1] Colorless plates mp 235—237 °C (dec.), which was identified as **4** on comparing the IR and NMR spectral data with those of **4**.[4]

5β-Chloro-4α-methoxysantonin (6) This was prepared as described in the literature.[1] Colorless plates. mp 216—219 °C.

Santonin α-Epoxide (5) This was prepared in a manner similar to that described by Wedekind and Koch.[3] **5**: Colorless plates. mp 212—214 °C, [lit.,[3] mp 214 °C]. IR and NMR spectral data were identical with those reported.

1α,2β,4α,5β-Tetrachloro-1,2-dihydrosantonin (7) This was prepared as described in the literature.[2] mp 207—209 °C (dec.).

2,4α,5β-Trichlorosantonin (8) This was prepared as described in the literature[2] colorless plates mp 216—218 °C (dec.).

1α,2β,5β-Trichloro-1,2,-dihydro-4α-hydroxysantonin (9) Chlorine gas was passed into a solution of 1,2-dichlorosantonin (**2**) (4.0 g) in acetic acid (40 ml) and water (200 ml) with stirring at room temperature for 9.5 h. The precipitate was filtered off and washed with water. Crystallization from MeOH gave **9** (2.8 g, 59.6%) as colorless plates. mp 255—259 °C (dec.). IR ($CHCl_3$): 3620, 1786, 1755 cm^{-1}. UV λ_{max} nm (ε): 248 (1400). ^{1}H-NMR ($CDCl_3$) δ: 7.06 (1H, s, OH), 5.78 (1H, d, $J_{2,1}=12$ Hz, 2-H), 4.82 (1H, d, $J_{6,7}=11$ Hz, 6-H), 4.30 (1H, d, $J_{1,2}=12$ Hz, 1-H), 1.66 (3H, s, 4-CH_3), 1.54 (3H, s, 10-CH_3), 1.14 (3H, d, $J=6$ Hz, 11-CH_3). *Anal.* Calcd for $C_{15}H_{19}Cl_3O_4$: C, 48.74; H, 5.18; Cl, 28.77. Found: C, 48.63; H, 5.12; Cl, 28.95. MS *m/z*: 332 ($M^+ - HCl$).

1α,2β,5β-Trichloro-1,2-dihydro-4α-methoxysantonin (10) Dry chlorine was passed into a solution of 1,2-dichlorosantonin (**2**) (2.0 g) in MeOH (100 ml) for 40 min at room temperature. The solvent was removed by evaporation under reduced pressure. Compounds **2**, **11**, and **10** were found in the resulting oil by thin layer chromatography (TLC) and NMR spectral examination. The oil was chromatographed over silica gel. Elution with benzene gave **10** (0.1 g), which was crystallized from MeOH as colorless plates. mp 216—219 °C (dec.). IR (KBr): 1782, 1753 cm^{-1}. UV λ_{max} nm (ε): 252 (400), 306 (60). ^{1}H-NMR ($CDCl_3$) δ: 5.21 (1H, d, $J_{2,1}=12$ Hz, 2-H), 4.49 (1H, d, $J_{6,7}=12$ Hz, 6-H), 4.28 (1H, d, $J_{1,2}=12$ Hz, 1-H), 3.15 (3H, s, $-OCH_3$), 1.75 (3H, s, 4-CH_3), 1.57 (3H, s, 10-CH_3), 1.26 (3H, d, $J=7$ Hz, 11-CH_3). *Anal.* Calcd for $C_{16}H_{21}Cl_3O_4$: C, 50.09; H, 5.41; Cl, 27.72. Found: C, 50.24; H, 5.41; Cl, 27.50. MS *m/z*: 382 (M^+).

1β,2α,5α-Trichloro-1,2-dihydro-4α-methoxysantonin (13) Dry chlorine was passed into a mixture of **6** (2.5 g), acetic acid (40 ml) and chloroform (40 ml) for 12 h at room temperature. The solvent was evaporated off *in vacuo* and the residue was extracted with chloroform. After washing with water and drying over calcium chloride, the extract was evaporated under reduced pressure and the residue was crystallized from MeOH, giving **16** (1.4 g) (45.2%) as colorless prisms. mp 243—245 °C (dec.). IR ($CHCl_3$): 1783, 1730 cm^{-1}. UV λ_{max} nm (ε): 252 (1700), 328 (40). ^{1}H-NMR ($CDCl_3$) δ: 4.73 (1H, d, $J_{2,1}=6$ Hz, 2-H), 4.56 (1H, d, $J_{1,2}=6$ Hz, 1-H), 4.55 (1H, d, $J_{6,7}=12$ Hz, 6-H), 3.15 (3H, s, $-OCH_3$), 1.74 (3H, s, 4-CH_3), 1.55 (3H, s, 10-CH_3), 1.25 (3H, d, $J=7$ Hz, 11-Me). *Anal.* Calcd for $C_{16}H_{21}Cl_3O_4$: C, 50.09; H, 5.52; Cl, 27.72. Found: C, 50.03; H, 5.52; Cl, 27.54. MS *m/z*: 382 (M^+).

2,5β-Dichloro-4α-methoxysantonin (11) (a) Preparation from 2-Chlorosantonin (**3**): Dry chlorine was passed into a solution of 2-chlorosantonin (0.9 g) in MeOH (30 ml) for 30 min at room temperature. MeOH was removed *in vacuo*. The residue was found to be a mixture of **3** and **11**. The residue was chromatographed over silica gel. Elution with chloroform gave **11** (0.2 g), which was crystallized from MeOH as colorless plates. mp 210—213 °C (dec.). IR ($CHCl_3$): 1780, 1709, 1621 cm^{-1}. UV λ_{max} nm (ε): 253 (4700). ^{1}H-NMR ($CDCl_3$) δ: 6.52 (1H, s, 1-H), 4.42 (1H, d, $J_{6,7}=12$ Hz, 6-H), 3.10 (3H, s, $-OCH_3$), 1.74 (3H, s, 4-CH_3), 1.51 (3H, s, 10-CH_3), 1.25 (3H, d, $J=6$ Hz, 11-CH_3). *Anal.* Calcd for $C_{16}H_{20}Cl_2O_4$: C, 55.34; H, 5.81; Cl, 20.42. Found: C, 55.20; H, 5.79; Cl, 20.32. MS *m/z*: 346 (M^+).

(b) Preparation from 1β,2α,5β-Trichloro-4α-methoxysantonin (**13**): A mixture of **13** (0.5 g) and aniline (5.0 ml) in MeOH (50 ml) was refluxed for 1 h, and the solvent was removed *in vacuo*. The excess of aniline was neutralized with 5% hydrochloric acid and the mixture was extracted with chloroform. The extract was dried over anhydrous calcium chloride. After evaporation of chloroform, the remaining solid was crystallized from MeOH, to give **11** (0.4 g) (88.9%). This was identical to the sample obtained from 2-chlorosantonin, by comparisons of IR and NMR spectra and a mixed melting point determination.

(c) Preparation from 1α,2β,5β-Trichloro-4α-methoxysantonin (**10**): A mixture of **10** (40 ml) and aniline (1.0 ml) in MeOH (5.0 ml) was refluxed for 2 h. After removal of MeOH *in vacuo*, the excess of aniline was neutralized with 5% hydrochloric acid and extracted with chloroform. The extract was dried and evaporated to give the residue, which was crystallized from MeOH to give **12** (20 mg). Examination of the IR and NMR

Table I. Final Atomic Coordinates ($\times 10^4$), and Equivalent Isotopic Temperature Factors (B_{eq}/Å^2) of Non-hydrogen Atoms, with Estimated Standard Derivations in Parentheses, for 1α,2α,5β-Trichloro-4α-methoxysantonin (**13**)

Atom	X	Y	Z	B_{eq}(Å^2)
Cl 1	6510 (3)	5555 (2)	4302 (4)	6.8
Cl 2	6662 (2)	5705 (2)	870 (4)	5.3
Cl 3	4639 (2)	8209 (2)	3574 (3)	3.6
O 1	4273 (5)	6833 (4)	360 (8)	4.1
O 2	6307 (4)	9590 (3)	2352 (7)	3.0
O 3	7082 (6)	10813 (4)	1625 (8)	4.5
O 4	6742 (4)	7675 (4)	454 (6)	2.8
C 1	5897 (7)	6457 (5)	3413 (11)	3.1
C 2	5562 (7)	6185 (5)	1922 (11)	2.9
C 3	5097 (6)	6935 (5)	1119 (9)	2.4
C 4	5691 (6)	7809 (5)	1164 (9)	2.1
C 5	5989 (6)	8012 (4)	2729 (9)	1.9
C 6	6702 (6)	8801 (5)	3014 (10)	2.4
C 7	7911 (6)	8733 (5)	2494 (10)	2.2
C 8	8507 (7)	8029 (5)	3307 (10)	3.1
C 9	7845 (6)	7194 (5)	3119 (10)	2.6
C 10	6606 (7)	7275 (5)	3612 (10)	2.6
C 11	8247 (6)	9686 (5)	2741 (11)	3.0
C 12	7203 (7)	10118 (5)	2174 (11)	3.2
C 13	9308 (8)	9945 (6)	1880 (12)	4.5
C 14	4985 (8)	8491 (6)	406 (13)	4.1
C 15	6610 (9)	7460 (7)	5250 (9)	3.8
C 16	6703 (9)	7547 (8)	−1098 (11)	4.6

Table II. Bond Lengths (l/Å) and Angles (ϕ/°) with Estimated Standard Deviations in Parentheses

Cl 1–C 1	1.796 (9)	O 1–C 3–C 4	120.2 (7)
Cl 2–C 2	1.811 (9)	C 2–C 3–C 4	120.5 (6)
Cl 3–C 5	1.830 (7)	O 4–C 4–C 3	105.3 (6)
O 1–C 3	1.229 (10)	O 4–C 4–C 5	105.4 (5)
O 2–C 6	1.460 (9)	O 4–C 4–C14	111.8 (6)
O 2–C12	1.367 (9)	C 3–C 4–C 5	108.4 (6)
O 3–C12	1.211 (10)	C 3–C 4–C14	110.4 (6)
O 4–C 4	1.442 (8)	C 5–C 4–C14	115.1 (6)
O 4–C16	1.467 (11)	Cl 3–C 5–C 4	103.9 (4)
C 1–C 2	1.514 (14)	Cl 3–C 5–C 6	106.6 (5)
C 1–C10	1.548 (11)	Cl 3–C 5–C10	107.9 (5)
C 2–C 3	1.501 (11)	C 4–C 5–C 6	117.6 (6)
C 3–C 4	1.543 (10)	C 4–C 5–C10	116.7 (6)
C 4–C 5	1.541 (11)	C 6–C 5–C10	103.4 (6)
C 4–C14	1.536 (12)	O 2–C 6–C 5	115.3 (6)
C 5–C 6	1.526 (10)	O 2–C 6–C 7	103.4 (6)
C 5–C10	1.600 (10)	C 5–C 6–C 7	114.8 (6)
C 6–C 7	1.535 (10)	C 6–C 7–C 8	109.7 (6)
C 7–C 8	1.518 (11)	C 6–C 7–C11	97.5 (6)
C 7–C11	1.562 (11)	C 8–C 7–C11	119.8 (6)
C 8–C 9	1.539 (11)	C 7–C 8–C 9	108.4 (6)
C 9–C10	1.563 (11)	C 8–C 9–C10	112.9 (6)
C 10–C15	1.560 (12)	C 1–C10–C 5	106.2 (6)
C 11–C12	1.520 (11)	C 1–C10–C 9	114.9 (6)
C 11–C13	1.561 (13)	C 1–C10–C15	105.9 (7)
C 6–O 2–C12	107.9 (5)	C 5–C10–C 9	110.3 (6)
C 4–O 4–C16	116.6 (6)	C 5–C10–C15	112.1 (6)
Cl 1–C 1–C 2	108.4 (5)	C 9–C10–C15	107.6 (7)
Cl 1–C 1–C10	111.6 (6)	C 7–C11–C12	99.2 (6)
C 2–C 1–C10	119.3 (7)	C 7–C11–C13	112.5 (6)
Cl 2–C 2–C 1	115.1 (6)	C 12–C11–C13	112.2 (7)
Cl 2–C 2–C 3	108.9 (6)	O 2–C12–O 3	120.0 (7)
C 1–C 2–C 3	109.9 (6)	O 2–C12–C11	109.8 (6)
O 1–C 3–C 2	119.2 (7)	O 3–C12–C11	130.3 (7)

Table III. Selected Torsional Angles (ϕ/°) with Estimated Standard Deviations in Parentheses

C 1–C 2–C 3–C 4	−45.3 (10)
C 2–C 3–C 4–C 5	46.6 (9)
C 3–C 4–C 5–C 10	−49.3 (8)
C 4–C 5–C10–C 1	51.2 (8)
C 5–C10–C 1–C 2	−50.5 (9)
C 10–C 1–C 2–C 3	48.0 (10)
Cl 1–C 1–C 2–Cl 2	53.9 (8)
Cl 3–C 5–C 4–O 4	−178.3 (5)
Cl 3–C 5–C 4–C 14	−54.7 (8)
Cl 2–C 2–C 3–O 1	−94.3 (8)
O 4–C 4–C 3–O 1	110.1 (8)
H 1–C 1–C 2–H 2	75 (6)

spectra and a mixed melting point determination showed that this compound was **12**.

2,5β-Dichloro-4α-hydroxysantonin (12) (a) Preparation from 1α,2β,5β-Trichloro-1,2-dihydro-4α-hydroxysantonin (**9**): A mixture of **9** (1.0 g) and aniline (10 ml) in MeOH (100 ml) was refluxed for 10 min. After evaporation of the solvent, the excess of aniline was neutralized with 5% hydrochloric acid and the mixture was extracted with chloroform. After removal of the dried chloroform, the residue was crystallized from MeOH to give **12** (0.7 g) (78%) as colorless plates. mp 251—255 °C (dec.). IR (KBr): 3450, 1782, 1701, 1626 cm^{-1}. UV λ_{max} nm (ε): 253 (4100). ^{1}H-NMR ($CDCl_3$) δ: 6.88 (1H, s, 1-H), 6.72 (1H, s, OH), 4.71 (1H, s, $J_{6,7}=11$ Hz, 6-H), 1.64 (3H, s, 4-CH_3), 1.48 (3H, s, 10-CH_3), 1.14 (3H, d, $J=6$ Hz, 11-CH_3). *Anal.* Calcd for $C_{15}H_{18}Cl_2O_4$: C 54.07; H, 5.45; Cl, 21.28. Found: C, 53.80; H, 5.10; Cl, 21.35. MS m/z: 332 (M^+).

(b) Preparation from 2-Chlorosantonin (**3**): Dry chlorine gas was passed into a solution of 2-chlorosantonin (1.0 g) in acetic acid (10 ml) and water (300 ml) for 12 h at room temperature. A precipitate was collected, washed with water and dried. Crystallization from MeOH gave **12** (0.3 g). Examination of the IR and NMR spectra and a mixed melting point determination showed that this compound was **12**.

(c) Preparation from Santoninchlorohydrin (**4**): Dry chlorine gas was passed into a solution of **4** (1.0 g) in chloroform (100 ml) and acetic acid (10 ml) at room temperature. After evaporation of a large portion of the solvent *in vacuo*, water (100 ml) was added. The resulting precipitate was filtered, washed with water and dried. The precipitate was found to be a mixture of **4**, **12**, and **16** by TLC and NMR spectral examination. The dried precipitate was chromatographed over silica gel. Elution with chloroform gave **12** (0.3 g). Examination of the IR and NMR spectra and a mixed melting point determination showed that this compound was **12**. 1α,2α,5β-Trichloro-1,2-dihydro-4α-hydroxysantonin (**16**): ^{1}H-NMR ($CDCl_3$) δ: 5.06 (1H, d, $J_{1,2}=6$ Hz, 1-H), 4.63 (1H, d, $J_{2,1}=6$ Hz, 2-H), 4.55 (1H, d, $J_{6,7}=11$ Hz, 6-H).

2-Chloro-4,5-epoxysantonin (15) Dry chlorine was passed into **5** (0.8 g) in acetic acid (30 ml) and chloroform (30 ml) as above for 10 h at room temperature. A large part of the solvent was evaporated off under reduced pressure. Addition of water (100 ml) gave a precipitate, which was filtered, washed with water and dried. This solid was found to be a mixture of **14** and **15** by TLC and NMR spectral examination. The dried precipitate was chromatographed over silica gel. Elution with chloroform gave **15** (0.3 g), which was crystallized from MeOH as colorless plates. mp 204—205 °C. IR (KBr): 1780, 1701, 1622 cm^{-1}. UV λ_{max} nm (ε): 221 (5200), 252 (7600). ^{1}H-NMR ($CDCl_3$) δ: 6.50 (1H, s, 1-H), 4.59 (1H, d, $J_{6,7}=10$ Hz, 6-H), 1.77 (3H, s, 4-CH_3), 1.35 (3H, s, 10-CH_3), 1.13 (3H, d, $J=6$ Hz, 11-CH_3). *Anal.* Calcd for $C_{15}H_{17}ClO_4$: C, 60.71; H, 5.78; Cl, 11.95. Found: C, 60.53; H, 5.70; Cl, 12.26. MS m/z: 296 (M^+). 1α,2α-Dichloro-1,2-dihydro-4,5-epoxysantonin (**14**): ^{1}H-NMR ($CDCl_3$) δ: 5.15 (1H, d, $J_{1,2}=2$ Hz, 1-H), 4.30 (1H, d, $J_{6,7}=10$ Hz, 6-H), 4.10 (1H, d, $J_{2,1}=2$ Hz, 2-H).

X-Ray Analysis of 13 X-Ray Crystallographic Analysis of **13**: A single crystal of **13** was grown in MeOH as a colorless plate with dimensions of $0.2\times0.3\times0.2$ mm^3. Crystal data and intensity data were collected on a Rigaku automated four-circle diffractometer using Cu K_α radiation ($\lambda=1.5479$ Å) monochromated by a graphite plate. $C_{16}H_{21}O_4Cl_3$ ($M_r=383.683$; orthorhombic, space group, $P2_12_12_1$, $Z=4$. Unit cell dimensions; $a=12.008$ (3), $b=15.643$ (3), $c=9.361$ (1) Å, $V=1758.4$ $Å^3$, $D_c=1.449$ $g\,cm^{-3}$, $\mu=5.372$ cm^{-1} for Cu K_α radiation. A total of 1536 non-zero independent reflections out of 1560 reflections within the range of $2\theta<140°$ were used for structure determination and refinement. Corrections were applied for Lorentz and polarization factors, but not for absorption and extinction. The structure was solved by the direct method using the MULTAN program,[5] followed by isotropic least-squares calculation, and subsequent difference Fourier synthesis located all the atoms of **13** except hydrogen atoms. Some hydrogen atoms were located on a difference map calculated from non-hydrogen atoms, but the hydrogen atoms attached to the methyl groups were generated computationally on the basis of stereochemical and geometrical considerations. Final $R\{=\sum(||F_o|-|F_c||)/\sum|F_o|\}$ value was 0.063 for observed reflections. Final atomic coordinates and equivalent isotropic temperature factors of non-hydrogen atoms of **13** are listed in Table I. Bond lengths and angles and selected torsional angles are given in Tables II and III. All calculations were carried out on a HITAC M-680H computer at the Computer Center of the University of Tokyo, using a local version of the UNICS program.[6] The atomic scattering factors were taken from the literature.[7]

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