Studies on the Chlorinated α-Santonins. III.[1] Revised Structure of α-Santonin Chlorohydrin

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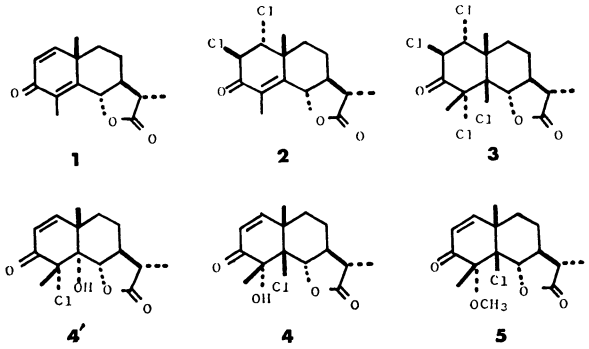
Synopsis. The molecular structure of α-santonin chlorohydrin is revised to 5β-chloro-4α-hydroxysantonin from 4α-chloro-5α-hydroxysantonin (Hendrickson and Bogard) by X-ray analysis of the corresponding 5β-chloro-4α-methoxysantonin.

Hendrickson and Bogard[2] have re-examined the products derived from chlorination, epoxidation and subsequent changes of α-santonin (**1**), and assigned structures to the various products. We have revised their structure of dichloro-α-santonin to **2**, based on an X-ray analysis of the derived tetrachloro-α-santonin (**3**).[3]

In this paper we wish to report a further revision, that of santonin chlorohydrin from **4'** to **4**, on the basis of an X-ray analysis of the related 5β-chloro-4α-methoxysantonin (**5**), and the ready conversion (HI, 90°) of **5** to **4**.



1 **2** **3**

4' **4** **5**

Experimental

5β-Chloro-4α-methoxysantonin (5). Dry chlorine was passed into α-santonin (5.0 g) in methanol (20 ml) at 0° for 20 min. The methanol was evaporated, and the residue was crystallized from methanol to give **5** (2.84 g) as colorless plates, mp 216—219 °C. Except for the unchanged material, no other isomeric products were found by TLC and NMR spectral examination of the residue. IR ($CHCl_3$) 1782, and 1691 cm^{-1}; UV(EtOH) λ_{max} 231 nm (ε=6300); NMR($CDCl_3$) δ 6.30 (1H, d, $J_{1,2}$=11 Hz, 1-H), 5.89 (1H. d, $J_{2,1}$=11 Hz, 2-H), 4.41 (1H, d, $J_{6,7}$=12 Hz, 6-H), 3.10 (3H, s, OMe), 1.69 (3H, s, 4-Me), 1.48 (3H, s, 10-Me), and 1.23 (3H, d, J=7 Hz, 11-Me). Found: C, 61.28; H, 6.88; Cl, 11.54%; M^+, 312. Calcd for $C_{16}H_{21}ClO_4$: C, 61.44; H, 6.77; Cl, 11.33%; M, 312.

5β-Chloro-4α-hydroxysantonin (4) from 5. A suspension of **5** (1.0 g) in 57% hydriodic acid (20 ml) was kept heating at 80—90 °C for 10 h. After filtrating the precipitate, water was added to the filtrate to give a crystalline precipitate, which was dried and chromatographed over silica gel. Elution with chloroform gave **4** (0.2 g), which was recrystallized from methanol to give colorless plates, mp and mixed mp 235—237 °C (dec) with the products prepared by Wedekind and Tettweiler.[4] The IR and NMR spectra of the two samples were identical. No other isomeric products except the unchanged starting material were found by TLC and NMR spectral examination of the mother liquor.

Crystallographic Measurement. The crystal of **5** belongs to the orthorhombic space group $P2_12_12_1$, a=8.458 (7), b=27.100 (8), c=6.796 (3) Å, Dm=1.34 g cm^{-3}, Dc=1.334 g cm^{-3}, and Z=4. The three-dimensional intensity data were collected on a Rigaku automatic four-circle diffractometer with graphite monochromated Cu $K\alpha$ radiation . Reflections having an intensity exceeding the corresponding standard deviations by a factor of three were treated as observed. 981 reflections with $2\theta \leqq 139°$ were retained and corrected for Lorentz and polarization factors but not for absorption and extinction factors.

Determination and Refinement of the Structure. The structure was determined by the heavy atom method. From the three-dimensional Patterson map, the position of the chlorine atom was easily deduced. From the Fourier synthesis with the chlorine phases, all the 20 non-hydrogen atoms in the asymmetric unit were obtained. The oxygen atoms were identified by structural consideration. Refinement of atomic parameters was carried out by the block-diagonal least-squares method, the quantity minimized being $\sum\omega(|F_o|-|E_c|)^2$, with ω=1.0 for all the reflections used . All the hydrogen atoms except the 12 hydrogen atoms on the methyl groups were located on the difference map. The final R value was 0.081.

TABLE 1. FINAL ATOMIC PARAMETERS (×10⁴) AND THERMAL PARAMETERS

Standard deviations are given in parentheses. The B_{eq} values are the equivalent isotropic temperature factors.[a]

Atom	x	y	z	B_{eq}/Å²
Cl	5687(4)	3755(1)	7537(5)	5.9
C(1)	6714(16)	4663(4)	4369(19)	4.1
C(2)	5195(16)	4797(4)	4699(22)	4.2
C(3)	3923(15)	4439(4)	4931(17)	4.3
C(4)	4250(14)	3925(4)	4111(15)	4.4
C(5)	5946(14)	3765(4)	4894(13)	3.8
C(6)	6538(13)	3247(3)	4355(15)	2.8
C(7)	6997(12)	3187(4)	2193(15)	2.9
C(8)	8418(15)	3522(4)	1752(18)	4.3
C(9)	7966(14)	4060(4)	2153(19)	3.3
C(10)	7291(14)	4142(4)	4408(17)	3.8
C(11)	7159(13)	2626(4)	2110(19)	3.4
C(12)	5813(15)	2482(4)	3510(17)	3.0
C(13)	8760(15)	4107(5)	5811(21)	5.0
C(14)	2909(13)	3546(4)	4628(22)	2.8
C(15)	7028(18)	2392(5)	51(22)	6.0
C(16)	3067(17)	4190(6)	1050(19)	7.1
O(1)	2653(10)	4550(3)	5680(14)	5.4
O(2)	5492(9)	2845(3)	4738(11)	3.9
O(3)	5085(10)	2100(3)	3450(14)	4.0
O(4)	4403(9)	3969(3)	2006(10)	4.5

a) W.C. Hamilton, *Acta Crystallogr.*, **12**, 609 (1959).

TABLE 2. BOND LENGTHS AND BOND ANGLES
Standard deviations are given in parentheses.

Bond lengths (l/Å)			
C(1)–C(2)	1.35(2)	C(7)–C(8)	1.54(2)
C(1)–C(10)	1.49(2)	C(7)–C(11)	1.53(1)
C(2)–C(3)	1.46(2)	C(8)–C(9)	1.53(2)
C(3)–C(4)	1.53(2)	C(9)–C(10)	1.65(2)
C(3)–O(1)	1.23(2)	C(10)–C(13)	1.57(2)
C(4)–C(5)	1.59(2)	C(11)–C(12)	1.53(2)
C(4)–C(14)	1.57(2)	C(11)–C(15)	1.54(2)
C(4)–O(4)	1.44(2)	C(12)–O(2)	1.32(1)
C(5)–C(6)	1.54(2)	C(12)–O(3)	1.21(1)
C(5)–C(10)	1.56(2)	C(16)–O(4)	1.43(2)
C(6)–C(7)	1.53(2)	C(5)–Cl	1.81(1)
C(6)–O(2)	1.43(2)		
Bond angles (ϕ/°)			
C(10)–C(1)–C(2)	124(1)	C(7)–C(8)–C(9)	109(1)
C(1)–C(2)–C(3)	123(1)	C(8)–C(9)–C(10)	112(1)
C(2)–C(3)–C(4)	116(1)	C(1)–C(10)–C(5)	113(1)
C(2)–C(3)–O(1)	122(1)	C(1)–C(10)–C(9)	103(1)
C(4)–C(3)–O(1)	122(1)	C(1)–C(10)–C(13)	109(1)
C(3)–C(4)–C(5)	107(1)	C(5)–C(10)–C(9)	111(1)
C(3)–C(4)–C(14)	113(1)	C(5)–C(10)–C(13)	114(1)
C(3)–C(4)–O(4)	108(1)	C(9)–C(10)–C(13)	106(1)
C(5)–C(4)–C(14)	114(1)	C(7)–C(11)–C(12)	99(1)
C(14)–C(4)–O(4)	106(1)	C(7)–C(11)–C(15)	116(1)
C(4)–C(5)–C(6)	118(1)	C(12)–C(11)–C(15)	114(1)
C(4)–C(5)–C(10)	114(1)	C(11)–C(12)–O(2)	111(1)
C(6)–C(5)–C(10)	108(1)	C(11)–C(12)–O(3)	125(1)
C(5)–C(6)–C(7)	114(1)	O(2)–C(12)–O(3)	124(1)
C(5)–C(6)–O(2)	117(1)	C(4)–O(4)–C(16)	115(1)
C(6)–C(7)–C(8)	109(1)	C(4)–C(5)–Cl	103(1)
C(8)–C(7)–C(11)	121(1)	C(10)–C(5)–Cl	108(1)
C(7)–C(6)–O(2)	105(1)	C(6)–C(5)–Cl	105(1)
C(5)–C(4)–O(4)	106(1)		

The final atomic parameters are given in Table 1. Anisotropic thermal parameters of non-hydrogen atoms and atomic parameters of hydrogen atoms and the complete Fo–Fc data are kept at the Chemical Society of Japan (Document No. 8131).

Results and Discussion

A perspective view of the molecule with numbering of the atoms is given in Fig. 1. The bond lengths and angles are given in Table 2. No abnormal lengths and angles were found in the structure.

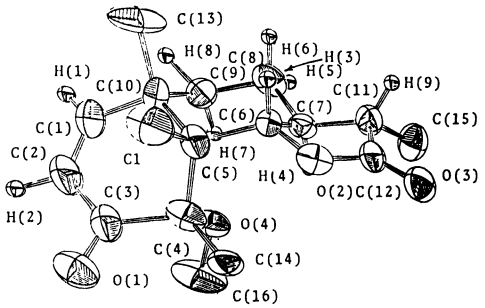


Fig. 1.

References

1) Part II: H. Takayanagi, H. Ogura, and Y. Iitaka, *Chem. Pharm. Bull.* (*Tokyo*), **26**, 2729 (1978).
2) J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc.*, **1962**, 1678.
3) H. Ogura, H. Takayanagi, A. Yoshino, and T. Okamoto *Chem. Pharm. Bull.* (*Tokyo*), **22**, 1433 (1974).
4) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 387, 1796 (1931).