239. Hiroshi Mitsuhashi : Crystallographic Study of Crude Drug
 Componentes. IV¹⁾. On the Configuration of Hyposantonin,
 Isohyposantonin and Its Derivatives. (2).

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On the basis of the results of the previous report¹⁾ establishing stereochemical relationship between santonin and its derivatives, it was found that, in respect to the steric configuration, isohyposantonin corresponds to *l*- α -desmotroposantonin, and the author attempted to determine the steric conversion of isohyposantonin expecting similar results, as had been obtained with desmotroposantonin. However, on treatment with various concentrations of sulfuric acid or absolute formic acid, it was found that isohyposantonin did not exhibit similar conversion.

According to Huang Minlon²⁾, the inversion of the asymmetric centers at C-5 and C-6 in *l*- α - or *d*- α -D.S., which occurs by the action of conc. mineral acids, was explained as follows :

It seems that, in the case of desmotroposantonin, B form may readily convert into A-form, so we can obtain *d*- β - or *l*- β -desmotroposantonin as the reaction product.

However, in the case of isohyposantonin, B-form will seem to be more stable than A, since dihydrosantoninic acid is obtained by the action of conc. mineral acids.

As had been described in the previous report (*loc. cit.*), the difference between hypo- and isohyposantonin would be caused by the inversion of the steric configuration of H

Fig. 1A

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1) Part III This Journal, **71**, 1115 (1951).

2) Huang Minlon: J. Am. Chem. Soc., **70**, 611 (1948).

atom attached to the C-5 atom, and this fact was also proved, in the present study, by the fact that both hypo- and isohyposantonin converted into the same dihydrosantonic acid by the action of conc. H_2SO_4 . The crystallographical character of dihydrosantonic acid and infrared spectra of hypo- and isohyposantonin were determined (Fig. 1).

On treatment with potassium hydroxide dihydrosantonic acid was optically inactivated. By the study of the ultraviolet spectra (Fig. 2), it has been suggested that a racemization might have taken place.

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Experimental

Action of Sulfuric Acid on Hypo- and Isohyposantonin.

Powderd hypo- or isohyposantonin (1 g.) was added to a cold mixture of conc. H_2SO_4 (1~1.5 g.) and water (1 g.), and the mixture was heated in a water bath at 85° for 20 hours. The reaction mixture was diluted with water] forming [a resinous substance, which was extracted with dil. aq. NaOH. The product separated by acidification was recrystallized twice from ligroin, then from dilute alcohol to pale yellow, long prisms (0.7 g.), m.p. $115\sim117^\circ$, $[\alpha]_D^{18} + 60^\circ$ (in absolute alcohol). It gives no melting point depression when admixed with dihydrosantonic acid obtained by Gucci's method³⁹. It discolors KMnO_4 solution immediately and is soluble in 5% Na_2CO_3 . On treatment with diazomethane, dihydrosantonic acid yielded an oily substance. *Anal.* Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: C, 78.25; H, 7.82; Mol. wt., 230. Found: C, 78.04; H, 7.68, Mol. wt., 229.7.

Hydrogenation experiments—Using Pd-charcoal as a catalyst, dihydrosantonic acid (0.2 g) in methanol absorbed 21 cc. hydrogen (at 10°) (1.1 mole). The absorption ceased in 1 hour. After removal of the catalyst and the [solvent, the residue was recrystallized from hydrated alcohol to give colorless crystals, m.p. $95\sim97^\circ$. *Anal.* Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 77.58; H, 8.63. Found: C, 77.73; H, 8.79. This compound shows an optical activity.

Reacting of Potassium hydroxide on Dihydrosantonic acid

A mixture of dihydrosantonic acid (1 g.) and KOH (1 g) was heated in a test tube with an air condenser in an oil bath at $200\sim210^\circ$ for 1 hour, water was evaporated during the process, and a dark brown residue was left, which was dissolved in water, and the solution acidified. The precipitate formed was crystallized twice from hydrated alcohol, then from ligroin, giving 0.6~0.7 g. of pale yellow crystals, m.p. 85° , $[\alpha]_D = 0^\circ$. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_2$: C, 78.25; H, 7.82; Mol. wt., 230. Found: C, 78.33; H, 7.62; Mol. wt., 228.

Hydrogenation—Using Pd-charcoal as a catalyst, activated dihydrosantonic acid (0.095 g.) in methanol absorbed 12 cc. hydrogen (at 10°) equivalent to 1.2 mols. After the excess of methanol was removed, the residue was crystallized from hydrated alcohol to yield colorless prisms, m.p. $85\sim86^\circ$. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 77.58; H, 8.63. Found: C, 78.63; H, 8.65.

This substance shows no optical activity.

Crystallographic Data

I. Optical character

Optical characters of active dihydrosantonic acid (from hypo-, isohyposantonin and Gucci's method) and its inactive form are as follows:

Dihydrosantonic acid	Refractive Index	Form	Crystal System	β -Angle	Axial Ratio	Optical Axial Angle
Active form	$\alpha = 1.4920$ $\beta = 1.6570$ $\gamma = 1.710$	Prism	Monoclinic	95°	0.6516:1: 0.5040	$2V = 68^\circ (-)$
Inactive form	$\alpha = 1.477$ $\beta = 1.710$ $\gamma = 1.743$	Plates	Monoclinic	95°	—	$2V = 77^\circ (-)$

II. Morphological character

Only crystals of the optically active form were measured on goniometer, those of the inactive form being too poorly developed.

Interfacial Angles

(Results of goniometry by a two-circle goniometer)

Form	S	Q	Obsvd.		Calcd.		No.
			ρ	φ	ρ	φ	
(120) m	S	C	90°00'	38°00'	90°00'	37°30'	4
(110) l	L	A	90°00'	56°55'	—	—	4
(100) a	M	A	90°00'	90°00'	90°00'	90°00'	2
(011) x	M	C	26°45'	10°00'	—	—	4
(031) f	L	C	56°40'	3°20'	56°40'	3°00'	4

Notes : S : Size of crystal faces VL, L, M, S.

Q : Degree of clearness of image A, B, C, D.

III. X-ray Data

The unit cells of these crystals were determined by the rotation method using K_{α} ($\lambda=1.540 \text{ \AA}$) with the results as follows :

Active form

Monoclinic $Z=4$ (There are 4 molecules in the unit cell)

$$a_0=10.32 \text{ \AA} \quad b_0=15.60 \text{ \AA} \quad c_0=7.82 \text{ \AA} \quad \beta=94^\circ$$

Inactive form

Monoclinic hemihedral $Z=4$

$$a_0=8.35 \text{ \AA} \quad b_0=14.75 \text{ \AA} \quad c_0=10.26 \text{ \AA} \quad \beta=95^\circ$$

IV. The piezoelectric properties were examined by means of the modified Giebe and Scheide method, which was developed lately in the Mineralogical Institute of the University. The result are as follows :

Optically inactive dihydrosantonin acid +

Summary

Hyposantonin and isohyposantonin do not undergo conversion such as that seen with desmotroposantonin by treatment with sulfuric acid, but yield dihydrosantonin acid. Those two compounds also undergo racemization by alkali fusion and yield optically inactive dihydrosantonin acid. It is assumed from the formation of dihydrosantonin acid that the steric difference between hypo- and isohypo-santonin is the difference in the position of the hydrogen atom attached to C_5 . Crystallographic measurements were made of optically active and inactive dihydrosantonin acids.

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