[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH INSTITUTE, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

SANTONIN AND RELATED COMPOUNDS.[1,2] IV. TETRAHYDROSANTONINS

MASAITI YANAGITA AND AKIRA TAHARA

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It is known (1) that *l*-santonin (I) readily take up two moles of hydrogen on catalytic hydrogenation to give tetrahydro compounds, producing two additional asymmetric centers in these molecules. Of the four possible stereoisomers of tetrahydrosantonin, two, the α-isomer, m.p. 156°, $[\alpha]_D$ +23.4° (in ethanol), and the β-isomer, m.p. 105°, $[\alpha]_D$ +9.3° (in methanol), are recorded in the literature (2). The above values for the α-isomer are generally accepted as authentic, though a variety of physical constants for this isomer previously have been reported by some workers (1). The isolation of the β-isomer was described only in the report of Wienhaus and Oettingen (2a). In the present work, we re-examined the separation of tetrahydro mixture of *l*-santonin, and the stereochemistry of santonin and the isolated tetrahydro compounds is discussed on the basis of experimental evidences.

Like the previous workers, we had difficulties in separating the tetrahydro isomers from the reduction mixture, and the relative amounts isolated were found to vary depending on small changes in the reaction conditions. After repeated recrystallizations of the mixture from ethanol a predominant isomer, whose physical constants are identical with those reported for the α-isomer, was obtained usually in a 11% yield. As the more-soluble crystals, a new isomer (IIb), m.p. 143–144°, $[\alpha]_D^{28}$ +64.5°, was isolated in a much smaller yield. However, attempts to obtain the so-called "β"-isomer of Wienhaus and Oettingen were unsuccessful. Although beautiful crystals with a melting point of approximately 105° was isolated in some steps of recrystallization of the tetrahydro mixture, this material did not show a constant melting point, and on further recrystallization, gave the above compound, m.p. 143–144°. From this, it is apparent that the so-called "β"-isomer of m.p. 105° is, in all probability, a tetrahydro mixture containing IIb. This consideration is supported by the fact that the reported melting point of a semicarbazone of the "β"-isomer is the same as that of the corresponding derivative of IIb. This isomer (IIb) is now designated as β-tetrahydrosantonin.

It was founded that the semicarbazone of β-tetrahydro compound on hydrolysis with dilute hydrochloric acid under milder condition did not regenerate the parent ketone, but gave the α-isomer (IIa). Consequently, it was assumed that the β-isomer itself can be converted to IIa by the similar procedure and this proved to be the case. When the crude tetrahydro mixture was similarly treated

[1] This title has been changed from ANALOGS OF SANTONIN. IV [cf. Part III: *J. Org. Chem.*, **19**, 1724 (1954)].

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with acid, the yield of α-tetrahydro compound separated was raised to 53%, and besides, the mother liquor of the α-isomer on prolonged standing at room temperature deposited a second new isomer, m.p. 96–97°, in a 16% yield. The latter is easily differentiated from the above isomers by its physical constants and the depressed mixture melting point. This new isomer is named γ-tetrahydrosantonin (IIc), which, as IIa, is unaffected by acid and is regenerated from its semicarbazone.

It has previously been reported (2c) that α-tetrahydrosantonin readily absorbs one mole of bromine to give the 2-bromo derivative (IIIa), m.p. 147° (decomp.). On treatment with γ-collidine at the reflux temperature, this bromide gave an 18% yield of mono-unsaturated compound (IVa), m.p. 139–140°, in which the location of the double bond between 1- and 2-positions is proved by the ultraviolet absorption spectrum, λ_{max}^{EtOH} 227 mμ, characteristic for α,β-unsaturated ketones with no substituents (3). Catalytic hydrogenation of the α-4,10-dihydro compound regenerated IIa, providing a support for the structure (IVa). Reaction of IIIa with Brady's reagent in methanol or ethanol solution respectively gave the 2,4-dinitrophenylhydrazone of the saturated compound carrying the corresponding alkoxyl group in place of the chlorine atom (Va, R = CH_3 or C_2H_5).

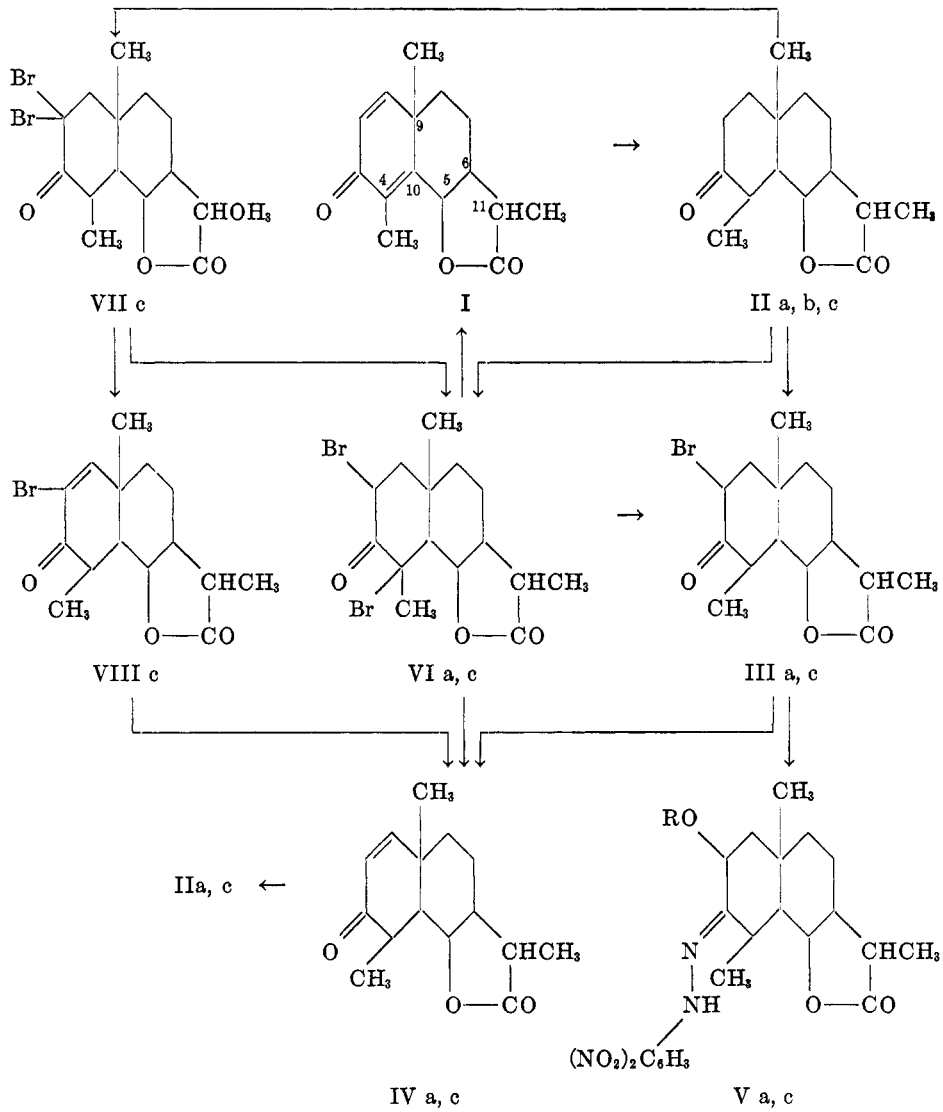
Monobromination of the γ-tetrahydro compound (IIc) took place less readily, compared with that of the α-isomer (IIa). The γ-bromo compound (IIIc), m.p. 144–146°, was obtained in 76% yield, which on collidine treatment gave γ-4,10-dihydrosantonin (IVc), m.p. 147–148°, in a better yield than that of IVa from IIIa. The γ-isomer is different from IVa, as shown by the mixture melting point determination, but exhibits an ultraviolet absorption maximum at 226 mμ, practically identical with that of IVa. It is evident that the double bond in IVc, as in IVa, must be located between the 1- and 2-positions, and therefore, IIc was monobrominated at the 2-position, as IIa. Conversion of γ-dihydro ketone (IVc) to IIc and γ-monobromide (IIIc) to the alkoxy compounds (Vc, R = CH_3 and C_2H_5) parallel the similar conversions of the corresponding α-isomers.

Catalytic hydrogenation of santonin is claimed (4) to give a dihydrosantonin, in which the double bond is situated between the 4- and 10-positions. For the purpose of comparison, various attempts were made to prepare the isomer with this double bond, but even with absorption of one mole of hydrogen in the presence of a basic catalyst poison, only the α-tetrahydro ketone, along with the starting material, was isolated from the hydrogenation mixture (5).

Contrary to the close parallelism observed in the above reactions (II → III → IV), the α- and γ-tetrahydro ketones behave quite differently in the dibromination and subsequent transformations.

The α-tetrahydro ketone (IIa) readily absorbed two moles of bromine in an ice-cooled chloroform solution to given an 85% yield of a dibromo derivative (VIa), m.p. 103–106° (decomp.). The yield and m.p. of this compound varies depending on the conditions under which the reaction takes place. When dibromination was carried out at a room temperature, the dibromide was not isolated, and in its stead, the monobromide (IIIa) was obtained in a poor yield. Such a facile

removal of the tertiary bromine atom at the 4-position in VIa was also caused by the base under mild conditions. When VIa was allowed to stand with collidine at a room temperature, the α-monobromide (IIIa) was obtained in a 27 % yield, along with a viscous oil which on further treatment with hot collidine gave a small amount of *l*-santonin, isolated as its 2,4-dinitrophenylhydrazone.



Reaction of α-dibromide (VIa) with collidine at the reflux temperature resulted in the formation of *l*-santonin and the α-dihydro ketone (IVa), each of which was isolated only as the 2,4-dinitrophenylhydrazone after chromatography. In addition, a trace of crystalline product, an isomer of santonin, m.p.

250–252°, was obtained, which, though its m.p. is close to that of *d*-desmotroposantonin (6), is different from it, and was not further investigated.

Dibromination of the γ-tetrahydro ketone (IIc) proceeded less readily than that of IIa and gave a 73% yield of the γ-dibromide (VIIc), m.p. 118–122°. Collidine treatment of VIIc at the reflux temperature yielded, with the formation of 1.27 equivalents of hydrogen bromide, a monobromodihydro ketone as the sole product. This compound was assigned the structure VIIIc on the basis of its ultraviolet absorption maximum at 252 mμ, which showed the bathochromic shift (26 mμ) characteristic for the Δ^1-2-bromo-3-ketone moiety (7). Reduction of the monobromodihydro compound with zinc and ethanol gave IVc, affording support for the structure VIIIc. It is evident, therefore, that the γ-dibromo compound has the *gem*-dibromo structure VIIc.

When the dibromination mixture of IIc was stored in a refrigerator, there was obtained, in 36% yield, a 2,4-dibromo compound (VIc), m.p. 115–117°, instead of VIIc. The 2,4-dibromide which is more stable than VIa and VIIc was reacted with hot collidine to give *l*-santonin, as crystals, in a better yield than VIa. This result proves the location of bromine atoms in VIc, and it is obvious that one bromine atom at the 2-position in VIIc readily migrates to the 4-position in the presence of hydrogen bromide.

Completion of interconversion of *l*-santonin (I) and the tetrahydro compounds clearly demonstrates that no changes of configuration take place at the asymmetric centers at the 5-, 6-, 9-, and 11-positions in these molecules during the transformations. Therefore, it is evident that three stereoisomers of the tetrahydrosantonins must differ in the spatial arrangements of the asymmetric centers at the 4- and 10-positions.

In view of the fact that in the systems containing two fused six-membered rings with an angular methyl group the spatial arrangement in the ring junctures is quite stable to acid (8), it can be deduced that the facile isomerization of the β-tetrahydro compound (IIb) to the α-isomer (IIa) with acid involves the change in the configuration of the methyl group at the 4-position, in which the axial substituent, being situated on the α-position to the carbonyl group, is expected to be easily epimerized. Thus, the methyl group at the 4-position must occupy an equatorial conformation in IIa and an axial conformation in IIb. For the same reason, the methyl group at the same position in IIc, which is unaffected by acid, must be equatorial-oriented, as in IIa.

From the above considerations, it becomes obvious that the isomerism of the α- and γ-tetrahydro compounds is dependent on the configuration at the 10-position. It is known (8, 9) that on catalytic hydrogenation under the usual conditions, compounds containing the Δ^4-3-ketoöctalin system generally afford a stereoisomeric mixture, of which an isomer of the *cis*-decalin type is almost invariably predominant. On analogy with this fact, it can be assumed that IIa, the predominant hydrogenation product of I, has a *cis* relationship of the two cyclohexane rings, while IIc has a *trans* relationship.

This configurational assignment is strongly supported on the following three grounds. First, the above cited situation that α-tetrahydro ketone (IIa) and its

TABLE I

MOLECULAR ROTATION DIFFERENCES BETWEEN ISOMERS OF THE α(AND β)- AND γ-SERIES

Compounds	C_{10}-H/ C_9-CH_3	$[\alpha]_D$	M_D	M_D (*cis*) − M_D (*trans*)
α-Tetrahydrosantonin (IIa)	*cis*	+23.4	+58.5	+40.3
β-Tetrahydrosantonin (IIb)	*cis*	+64.5	+161.3	+143.1
γ-Tetrahydrosantonin (IIc)	*trans*	+7.28	+18.2	
α-2-Bromotetrahydrosantonin (IIIa)	*cis*	+8.18	+26.9	+51.7
γ-2-Bromotetrahydrosantonin (IIIc)	*trans*	−7.55	−24.8	
α-4,10-Dihydrosantonin (IVa)	*cis*	+1.74	+4.3	+71.5
γ-4,10-Dihydrosantonin (IVc)	*trans*	−27.1	−67.2	
α-2-Methoxytetrahydrosantonin (Va)	*cis*	+74.5	+208.6	+392.8
γ-2-Methoxytetrahydrosantonin (Vc)	*trans*	−65.8	−184.2	
α-2-Ethoxytetrahydrosantonin (Va)	*cis*	+70.4	+207.0	+356.7
γ-2-Ethoxytetrahydrosantonin (Vc)	*trans*	−50.9	−149.7	

dibromide (VIa) are more reactive than the corresponding γ-isomers (IIc and VIc), is in accord with the finding (10) that *cis*-9-methyldecalin is thermodynamically unstable with respect to the *trans* isomer. Second, the formation of the *gem*-dibromo compound (VIIc) and its rearrangement into the *sym*-dibromo isomer (VIc), which reaction sequence was observed only in the γ-series, are comparable to the analogous transformations of 3-ketosteroids of allo series (rings A/B : *trans*) (11). Third, the compounds of the α- and β-series are invariably more dextrorotatory than the corresponding γ-isomer (Table I). This relationship bears resemblance to that in the steroids in which epimerization of C_5-H from the *cis* position with respect to the C_9-CH_3 group to a *trans* position is accompanied by a shift of rotation to the right (12).

The generalization (13) that 3-ketosteroids of the normal series (rings A/B : *cis*) are monobrominated exclusively at the 4-position, while those of the allo series brominate at the 2-position,[3] does not apply to the stereoisomers of tetrahydrosantonin (IIa and IIc), in both of which monobromination takes place exclusively at the 2-position, irrespective of the configuration of the ring junctures. The anomality in IIa seems to be attributable to the steric hindrance of the substituent at the 5-position. The equatorial methyl group at the 4-position in IIa cannot be connected with this anomality, since *cis*-4,9-dimethyl-3-decalone, where the methyl group at the same position is equatorial, was found to be monobrominated exclusively at the 4-position (14).

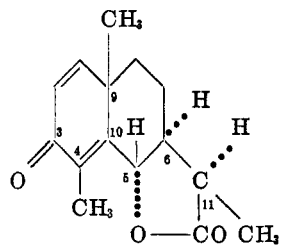
It is well established that the lactone in the santonin molecule is *trans*-fused

[3] It had previously been reported [Yanagita and Tahara: *J. Org. Chem.*, **18**, 792 (1953)] that *cis*-9-methyl-3-decalone was possibly brominated in the 2-position, but it seems more preferable to assign the 4-bromo structure for this bromide on the basis of the presence of a double bond between 4- and 10-positions in its dehydrobromination product reported there.

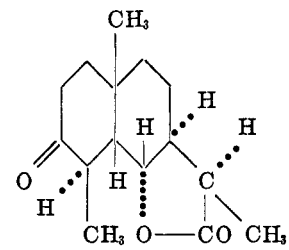
(15, 16). Examination of the molecular model shows that if the six-membered alicyclic ring takes a chair form, fusion of the lactone to this ring can only assume the equatorial-equatorial orientation. Thus, the lactone stands on the six-membered ring *trans* at the 5 position, and *cis* at the 6 position, to the angular methyl group.

Very recently, Corey[4] (17) proposed, mainly on the basis of the molecular rotation differences, the stereoformula (X) for *l*-santonin, where the methyl group at the 11-position is *cis* to the substituent at the 6-position.

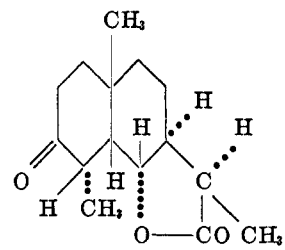
Based on the foregoing arguments about the configuration of tetrahydrosantonins and examination of the molecular models, the configurational structures XI, XII, and XIII are proposed respectively for α-, β-, and γ-tetrahydrosantonin (IIa, IIb, and IIc).



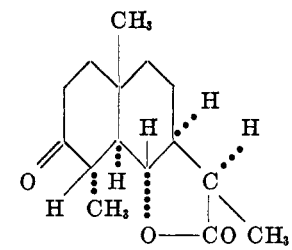
X



XI



XII



XIII

EXPERIMENTAL[5]

α- and β-Tetrahydrosantonin (IIa and IIb). A suspension of 15 g. of *l*-santonin,[6] m.p. 170–173°, $[\alpha]_D^{27}$ −169.5° (chloroform), λ_{max}^{EtOH} 240 mμ (logϵ 4.02), in 150 cc. of acetone was shaken in an atmosphere of hydrogen in the presence of palladium-carbon (prepared from

[4] After our manuscript was submitted for publication, this paper appeared, and in accordance with the suggestion of the deputy editor (Dr. Djerassi), the present paper was rewritten incorporating this new material. It was recorded (17) that Woodward and Yates [*Chemistry & Industry*, 1319, (1954)] reached the same conclusion about the stereoformula of santonin, but unfortunately their paper is not available to us.

[5] All melting points are not corrected. Optical rotation: unless otherwise noted, the sample was dissolved in ethanol to make a 1.5-cc. solution, and the rotation was determined in a 1-dm. semimicro tube. Microanalyses were carried out by Miss Shibuya of this laboratory: ultraviolet measurements were made by Miss Suzuki, in this school.

[6] This material was kindly supplied by Dr. K. Ueda, Fijisawa Pharmaceutical Industries, Ltd., Osaka, Japan.

10 cc. of 1% palladium chloride solution and 2.0 g. of carbon) until the hydrogen absorption ceased. Some 2950 cc. of hydrogen was rapidly absorbed, corresponding to two double bonds. Removal of the catalyst and distillation of the acetone quantitatively gave a crystalline mixture, m.p. 105–110° which was subjected to fractional crystallization from ethanol. The less-soluble crystals, α-tetrahydrosantonin (IIa), amounted to 1.7 g. (11%), and showed m.p. 153–154°, $[\alpha]_D^{27}$ +23.4° (54.14 mg. α +0.85°), λ_{max}^{EtOH} 286 mμ (log ε 1.16). Reported (2a), m.p. 156°, $[\alpha]_D$ +23.4°. It quantitatively formed a *semicarbazone*, m.p. 229–231° (decomp.), which was recrystallized from ethanol to platelets, m.p. 231–232°. Reported, m.p. 256–258° (10–20° below on slow heating) (2a).

Anal. Calc'd for $C_{16}H_{25}N_3O_3$: N, 13.67. Found: N, 13.38.

Attempts were made to separate the so-called "β"-isomer (2a) from the more-soluble fraction. There were obtained prisms, m.p. about 105°, and plates (β-isomer, 100 mg.), m.p. 143–144°, $[\alpha]_D^{28}$ +64.5° (58.1 mg.; α +2.5°), λ_{max}^{EtOH} 291.5 mμ (log ε 1.24). Recrystallization of the former crystals, which seem to correspond to the "β"-isomer, yielded the latter. The β-isomer showed obvious depression of the m.p. on admixture with the α-isomer.

Anal. Calc'd for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80.
Found: C, 72.02; H, 8.58.

IIb formed the *semicarbazone*, m.p. 254–256° (decomp.) (after recrystallization from a mixture of ethanol and chloroform).

Anal. Calc'd for $C_{16}H_{25}N_3O_3$: N, 13.69. Found: N, 13.44.

In one run, the crude tetrahydro mixture, obtained from 2 g. of santonin, was treated with a mixture of benzine and ether to give 0.80 g. of crystals, which on only one crystallization from dilute ethanol yielded 0.74 g. (37%) of pure α-tetrahydrosantonin, m.p. 152–153°.

Conversion of β-tetrahydrosantonin (IIb) *to α-isomer* (IIa). A mixture of 60 mg. of the semicarbazone of the β-isomer and 15 cc. of hydrochloric acid was heated on a boiling water-bath for 5 minutes. On cooling, the solution deposited platelets (35 mg., 72%), m.p. 147–149°, which on one recrystallization from dilute ethanol showed m.p. 152–153°, undepressed on admixture with the α-isomer (IIa).

The β-isomer (20 mg.) was warmed for 30 minutes with 2 cc. of 5% hydrochloric acid with the addition of a small quantity of ethanol. On cooling, there was obtained the α-isomer, m.p. and mixture m.p. 152–153°.

γ-Tetrahydrosantonin (IIc). To a warmed mixture of the crude tetrahydro product (prepared from 15.0 g. of santonin) and 30 cc. of 15% hydrochloric acid was added enough ethanol to form a solution, and the whole was refluxed for 1 hour. On cooling, the reaction mixture deposited 8 g. (53%) of α-tetrahydrosantonin (IIa) as platelets, m.p. and mixture m.p. 151–152°.

On allowing to stand at a room temperature for about 10 days, the mother liquor of IIa deposited 24 g. (16%) of prisms, m.p. 90–93°. Recrystallization from dilute ethanol raised the m.p. to 96–97°, $[\alpha]_D^{20}$ +7.28° (150.3 mg.; α +0.73°), λ_{max}^{EtOH} 286 mμ (log ε 1.25).

Anal. Calc'd for $C_{15}H_{22}O_3$: C, 72.00; H, 8.80.
Found: C, 71.52: H, 8.49.

It formed in 80% yield a *semicarbazone*, m.p. 240–242° (decomp.), which remained constant on recrystallization from ethanol. It showed an obvious depression of the m.p. with the semicarbazone of IIa or IIb. This derivative regenerated IIc on warming with 5% hydrochloric acid for 3 hours.

Anal. Calc'd for $C_{16}H_{25}N_3O_3$: N, 13.69. Found: N, 14.07.

α-2-Bromotetrahydrosantonin (IIIa). To a solution of 1.0 g. of IIa in 8 cc. of chloroform was added dropwise, with stirring, a solution of 0.64 g. of bromine in 5 cc. of chloroform with ice-cooling. After completion of the addition, stirring was continued for 15 minutes, and then a small quantity of ethanol was added. Most of the chloroform was removed under reduced pressure, and the solution which began to separate crystals was allowed to stand in a refrigerator overnight. There was obtained 1.16 g. (88%) of monobromide (IIIa), m.p. 140–141°, which was recrystallized from ethanol as thin platelets, m.p. 145–147° (decomp.),

$[\alpha]_D^{20}$ +8.18° (chloroform: 67.8 mg.; α +0.37°). Reported (2c), m.p. 147°, $[\alpha]_D$ +9.09° (chloroform).

α-2-Methoxytetrahydrosantonin (Va, R = CH_3). To a solution of 650 mg. of the above monobromide (IIIa) in a small quantity of methanol a solution of 2,4-dinitrophenylhydrazine (400 mg.) and 0.8 cc. of concentrated sulfuric acid in 6 cc. of methanol was added, and the 2,4-dinitrophenylhydrazone of the methoxy compound (Va, R = CH_3) separated immediately as yellow needles, m.p. 208–210°, (770 mg. 84%). Recrystallization from methanol raised the m.p. to 217–218°.

Anal. Calc'd for $C_{22}H_{28}N_4O_7$: N, 12.17. Found: N, 12.19, 11.90.

A mixture of 770 mg. of the above derivative, 2 cc. of pyruvic acid, and 45 cc. of 50% acetic acid was warmed on a boiling water bath for 1 hour. The solution was cooled, diluted with water, and extracted with chloroform. The extract was washed with 10% sodium hydroxide, dried, and evaporated to give 400 mg. of Va (R = CH_3), which was recrystallized with activated carbon from dilute ethanol to prisms (260 mg., 56%), m.p. 135–136°, $[\alpha]_D^{28}$ +74.5° (61.8 mg.; α +3.07°).

Anal. Calc'd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57.

Found: C, 68.33; H, 8.53.

α-2-Ethoxytetrahydrosantonin (Va, R = C_2H_5). When the above reaction was carried out in ethanol, the 2,4-dinitrophenylhydrazone of the ethoxy compound (Va, R = C_2H_5) was obtained in 84% yield as orange crystals, m.p. 224–225°. Recrystallization from ethanol raised the m.p. to 225–226°, depressed on admixture with the corresponding derivative of Va (R = CH_3).

Anal. Calc'd for $C_{23}H_{30}N_4O_7$: N, 11.81. Found: N, 12.07, 12.19.

On similar treatment with pyruvic acid, it gave the parent ethoxy compound (Va, R = C_2H_5), m.p. 158–160°, which was recrystallized from ethanol to orange crystals, m.p. 160–162°, $[\alpha]_D^{28}$ +70.4° (65.6 mg.; α +3.08°). It showed an obvious depression of the m.p. on admixture with the methoxy compound (Va, R = CH_3).

Anal. Calc'd for $C_{17}H_{26}O_4$: C, 69.29; H, 8.84.

Found: C, 69.25; H, 8.99.

α-4,10-Dihydrosantonin (IVa). The monobromide (IIIa, 860 mg.) was gently refluxed in 5 cc. of purified γ-collidine (b.p. 169–170°) for 15 minutes, and the reaction mixture was cooled, diluted with ether, and the collidine salt that separated (660 mg., 1.23 moles) was filtered off. After washing with dilute sulfuric acid and then with water, the ether solution was dried and evaporated, leaving a red oil (270 mg.), which on addition of a small quantity of ether, partly solidified on standing in a refrigerator. The solid (IVa) (110 mg., 18%), separated from the oil by suction, was recrystallized from diluted ethanol to elongated platelets, m.p. 139–140°, $[\alpha]_D^{28}$ +1.74° (43.18 mg.; α +0.05°), λ_{max}^{EtOH} 227 mμ (log ε 3.95).

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.07.

Found: C, 72.55; H, 7.91.

It formed a *2,4-dinitrophenylhydrazone*, as orange platelets, m.p. 250–251° (after recrystallization from ethanol).

Anal. Calc'd for $C_{21}H_{22}N_4O_6$: N, 13.08. Found: N, 13.41.

This regenerated IVa with pyruvic acid.

The above oil (160 mg.) on reaction with the Brady's reagent gave the 2,4-dinitrophenylhydrazone of IVa (145 mg., 8%).

Catalytic hydrogenation of IVa with palladium-carbon in ethanol gave α-tetrahydrosantonin (IIa), m.p. 153–154° (mixture m.p.).

γ-2-Bromotetrahydrosantonin (IIIc). A chloroform solution of 500 mg. of γ-tetrahydrosantonin (IIc) and 320 mg. of bromine was stirred and the reaction soon took place. The pale yellow solution was worked up as described for IIIa, giving 500 mg. (76%) of a monobromide (IIIc), m.p. 144–146° (decomp.). Recrystallization from ethanol gave needles, m.p. 147–149°, $[\alpha]_D^{20}$ −7.55° (chloroform: 70.45 mg.; α −0.355°).

Anal. Calc'd for $C_{15}H_{20}BrO_3$: C, 54.71; H, 6.37.

Found: C, 55.00; H, 6.32.

γ-2-Methoxytetrahydrosantonin (Vc, R = CH_3). This was prepared by the procedure described above for Va (R = CH_3). However, in this case, it was necessary to warm the methanol solution of IIIc for completion of the reaction. The 2,4-dinitrophenylhydrazone of Vc (R = CH_3), obtained in 72% yield, was recrystallized from ethanol to orange platelets, m.p. 196–197°.

Anal. Calc'd for $C_{22}H_{28}N_4O_7$: C, 68.78; H, 8.57; N, 12.17.

Found: C, 68.73; H, 8.78; N, 11.87.

With pyruvic acid, this derivative afforded in a 51% yield the γ-methoxy compound (Vc, R = CH_3), m.p. 160–162°, $[\alpha]_D^{14}$ −65.8° (36.9 mg.; α −1.62°), (after recrystallization from dilute ethanol).

Anal. Calc'd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57.

Found: C, 68.45; H, 8.41.

γ-2-Ethoxytetrahydrosantonin (Vc, R = C_2H_5). The above reaction was carried out in ethanol solution, giving the 2,4-dinitrophenylhydrazone of Vc (R = C_2H_5), m.p. 214–216°, in 70% yield. Recrystallization from ethanol gave yellow needles, m.p. 216–218°.

Anal. Calc'd for $C_{23}H_{30}N_4O_7$: N, 11.81. Found: N, 11.83.

This derivative gave, in 47% yield, the ethoxy compound (Vc, R = C_2H_5) m.p. 160–162°, $[\alpha]_D^{14}$ −50.9° (22.7 mg.; α −0.77°) (after recrystallization from dilute ethanol).

Anal. Calc'd for $C_{17}H_{26}O_4$: C, 69.29; H, 8.84.

Found: C, 69.01; H, 8.59.

γ-4,10-Dihydrosantonin (IVc). By the procedure described for IVa, γ-monobromide (IIIc, 400 mg.) was treated with collidine to give 120 mg. (36%) of IVc, m.p. 130–136°, with formation of 240 mg. (0.96 mole) of the collidine salt. In addition, the mother oil (180 mg.) of IVc gave 110 mg. of the 2,4-dinitrophenylhydrazone, m.p. 228–230° (mixture m.p. with the sample below) of IVc. The analytical sample of IVc was obtained by recrystallization from dilute ethanol as prisms, m.p. 151–153°, $[\alpha]_D^{23}$ −27.1° (55.12 mg.; α −0.994°), λ_{max}^{EtOH} 226 mμ (logϵ 3.87). It showed an obvious depression of the m.p. on admixture with IVa.

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.07.

Found: C, 72.50; H, 8.20.

It formed a *2,4-dinitrophenylhydrazone* as orange needles, m.p. 230–231° (after recrystallization from ethanol).

Anal. Calc'd for $C_{21}H_{22}N_4O_6$: N, 13.06. Found: N, 12.85.

Catalytic hydrogenation of IVc with palladium-carbon in ethanol gave IIc.

Attempted preparation of the reported dihydrosantonin. An ethanol solution of 500 mg. of santonin was shaken in the atmosphere of hydrogen with 100 mg. of 3% palladium-calcium carbonate, with the addition of 0.1 g. of quinoline, and one mole of hydrogen was absorbed in 3 hours. The reaction mixture was worked up in the usual manner to give a pale yellow oil (480 mg.), which soon solidified partly. The solid (170 mg., 37%) was repeatedly recrystallized from ethanol to give *l*-santonin, m.p. 156–167° (mixture m.p.). The oily fraction, on standing for a prolonged time, yielded a trace of α-tetrahydrosantonin (IIa), m.p. and mixture m.p. 145–150°, and from its mother liquor, the semicarbazone of IIa (100 mg.), m.p. and mixture m.p. 229–231°, was isolated.

α-2,4-Dibromotetrahydrosantonin (VIa). By the procedure described above for IIIa, 800 mg. of α-tetrahydrosantonin (IIa) was treated with 1.03 g. of bromine to yield 1.1 g. (85%) of the dibromide (VIa), m.p. 103–106° (decomp.). Recrystallization from ethanol gave needles, m.p. 105–110° (decomp.), $[\alpha]_D^{20}$ +64.4° (chloroform: 79.2 mg.; α +3.40°), $\lambda_{max}^{CHCl_3}$ 244.5 mμ (logϵ 2.95).

The variation in m.p. of the pure sample was observed even under the same reaction conditions, and hence, the grade of its purity was determined by elemental analysis.

Anal. Calc'd for $C_{15}H_{20}Br_2O_3$: C, 44.12; H, 4.91.

Found: C, 43.58, 43.41; H, 5.11, 4.66.

IIa (200 mg.) was brominated with 256 mg. of bromine at room temperature, and the reaction mixture, after addition of ethanol, was evaporated at about 60°. There was obtained 70 mg. (27%) of IIIa, m.p. 139–141° (decomp.) (after recrystallization from ethanol).

Anal. Calc'd for $C_{15}H_{21}BrO_3$: H, 54.71; H, 6.37.
Found: C, 54.81, 55.01; H, 6.47, 6.30.

For the purpose of comparison with the γ-dibromide (VIIc) described below, the brominated reaction mixture (VIa) was allowed to stand in a refrigerator overnight, and the solvent was removed at a reduced pressure to give the monobromide (IIIa), m.p. 137–140° (from ethanol) in a 30% yield.

Anal. Calc'd for $C_{15}H_{21}BrO_3$: C, 54.71; H, 6.37.
Found: C, 55.03; H, 6.28.

Reaction of the α-dibromide (VIa) *with γ-collidine. Formation of l-santonin* (I). *(a). At a high temperature.* A solution of 1.35 g. of VIa in 6 cc. of purified γ-collidine was refluxed in nitrogen atmosphere in an oil-bath for 50 minutes, and worked up as described for IVa. The collidine salt amounted to 1.42 g. (2.1 moles). The product was a dark red oil (600 mg.), which, on addition of a small amount of ethanol, solidified partly on standing. The solid (10 mg.), 235–238°, was recrystallized from ethanol as thin elongated prisms, m.p. 250–252° (sublim. at about 240°), λ_{max}^{EtOH} 232 mμ (log ε 4.08), 281.5 mμ (log ε 3.81). This is insoluble in 10% sodium hydroxide. It showed obvious depression of the m.p. with *d*-desmotroposantonin (m.p. 250–252°) (6).

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.31.
Found: C, 73.52; H, 7.40.

It showed no ketonic character.

The red oil, separated from the solid, gave a 2,4-dinitrophenylhydrazone (400 mg.), m.p. 140–150°, which was chromatographed on alumina (6 g., eluted with benzene). The crystals (180 mg., 11%), obtained from the initial fractions were combined and recrystallized from ethanol as deep red needles, m.p. 255–258°, which showed no depression of the m.p. on admixture with the 2,4-dinitrophenylhydrazone of *l*-santonin (I). The mother liquor of I yielded yellow platelets, m.p. 248–250°, which showed no depression on admixture with the 2,4-dinitrophenylhydrazone of α-4,10-dihydrosantonin (IVa).

(b). At room temperature. To 4 cc. of γ-collidine was added 350 mg. of VIa, and soon the collidine salt began to separate out. After standing at a room temperature for 1 hour, it was worked up as described for IVa. The collidine salt isolated amounted to 150 mg. (1.16 moles). The solid, separated from the oil, was recrystallized from ethanol to give 40 mg. of α-monobromide (IIIa), m.p. 130–136°, which on further treatment with hot collidine yielded α-dihydrosantonin (IIa), isolated as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 246–249°.

The mother liquor, a red oil (170 mg.), was further treated with hot collidine, and an oily product yielded 40 mg. of the 2,4-dinitrophenylhydrazone of *l*-santonin, which after chromatography on alumina and recrystallization from ethanol showed m.p. and mixture m.p. 262–264°.

γ-2,2-Dibromotetrahydrosantonin (VIIc). A chloroform solution of 500 mg. of IIc and 640 mg. of bromine was stirred at a room temperature, and as soon as the mixture became cloudy, it was immediately chilled in ice-water. After the solution became clear, the stirring was continued further at room temperature for 10 minutes. A pale yellow solution was worked up as described for VIa. There was obtained 600 mg. (73%) of the dibromide (VIIc), m.p. 118–122°. The m.p. was not raised by recrystallization from ethanol, and varied in different runs. The substance was unstable at room temperature; $[\alpha]_D^{23}$ −34.5° (chloroform: 83.5 mg.; α −1.92°), $\lambda_{max}^{CHCl_3}$ 247 mμ (log ε 2.97).

Anal. Calc'd for $C_{15}H_{20}Br_2O_3$: C, 44.12; H, 4.91.
Found: C, 43.98; H, 5.12.

γ-2-Bromo-4,10-dihydrosantonin (VIIIc). A solution of 600 mg. of the above dibromide (VIIc) in 5 cc. of collidine was refluxed for 50 minutes. After being worked up as described for IVa, the solid (130 mg.), m.p. 224–227°, separated from the red oil, was recrystallized from ethanol as needles, m.p. 236–238° (sublim.), $[\alpha]_D^{23}$ −34.54° (chloroform: 83.46 mg; α −1.923°), $\lambda_{max}^{CHCl_3}$ 252 mμ (log ε 3.81).

Anal. Calc'd for $C_{15}H_{19}BrO_3$: C, 55.11; H, 5.82.
Found: C, 55.12; H, 6.53.

A solution of 70 mg. of VIIIc in 5 cc. of absolute ethanol was refluxed with 700 mg. of acid-washed zinc dust for 6 hours. On cooling, the zinc was filtered off, the filtrate was concentrated under reduced pressure, water was added to the residue, and it was extracted with ether. The ether extract was dried and evaporated, leaving 50 mg. (96%) of crystals (IVc), m.p. 130–140°, which were recrystallized from dilute ethanol to prisms, m.p. and mixture m.p. 150–152°.

γ-2,4-Dibromotetrahydrosantonin (VIc). After completion of the above bromination, the pale yellow reaction mixture of VIIc (prepared from 500 mg. of IIc) was closely stoppered and kept in a refrigerator overnight. After being worked up as described for IIIa, there was obtained 290 mg. (36%) of VIc, m.p. 115–117°, which on recrystallization from ethanol showed the same m.p.; $[\alpha]_D^{20}$ −112.5° (chloroform: 42.1 mg.; α −3.15°), $\lambda_{max}^{CHCl_3}$ 250 mμ (logϵ 3.028), 252 mμ (logϵ 3.030).

Anal. Calc'd for $C_{15}H_{20}Br_2O_3$: C, 44.12; H, 4.91.

Found: C, 44.00; H, 4.88.

This is much more stable than VIId at a room temperature.

Reaction of γ-2,4-dibromotetrahydrosantonin (VIc) *with γ-collidine. Formation of l-santonin.* The above dibromide (VIc, 500 mg.) was dehydrobrominated by the procedure described for IVa. The collidine salt isolated amounted to 270 mg. (1.8 moles). The red oil (220 mg), obtained from the ether extract, gave 70 mg. (37%) of crystals which were chromatographed through alumina (2.5 g., eluted with benzene), and recrystallized from ethanol to 40 mg. of colorless platelets, m.p. 170–172°, $[\alpha]_D^{20}$ −165.0° (29.0 mg.; α −3.19°), λ_{max}^{EtOH} 240 mμ (logϵ 4.08). It showed no depression of the m.p. on admixture with *l*-santonin.

SUMMARY

1. Three forms of tetrahydrosantonin, α, β, and γ, were isolated. The β-isomer readily isomerized to the α-isomer.

2. On reaction with one mole of bromine, the α- and γ-tetrahydrosantonins (IIa and IIc), respectively yielded the α- and γ-2-bromo compounds (IIIa and IIIc), which were dehydrobrominated with collidine to the corresponding 4, 10-dihydrosantonins (IVa and IVc).

3. With two moles of bromine, the α-isomer gave an unstable 2,4-dibromide (VIa) which was dehydrobrominated to *l*-santonin, while the γ-isomer (VIc) yielded the 2,2-dibromide (VIIc), which was dehydrobrominated to γ-2-bromo-4,10-dihydrosantonin (VIIIc). The 2,2-dibromo compound readily underwent rearrangement to the 2,4-isomer (VIc), which in turn gave *l*-santonin on treatment with collidine.

4. Configurations of α-, β-, and γ-tetrahydrosantonin have been tentatively proposed.

SHINJUKU-KU
TOKYO, JAPAN

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