

volume of boiling water giving white needles, m.p. 134–136°, yield 2.44 g. (29%). A sample recrystallized a second time from boiling water had m.p. 136–137° (lit.⁹ 137–138°); infrared spectrum (CHCl_3), bands at 5.72 and 5.94 μ ; ultraviolet spectrum (95% EtOH), λ_{max} 220 $\text{m}\mu$ ($\log \epsilon$ 4.31) and 327 $\text{m}\mu$ ($\log \epsilon$ 1.48); molecular weight (isothermal distillation, CHCl_3 , 25°) 254; calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_8$, 246.

Dihydro- γ -metasantonin (IX).— γ -Metasantonin (0.25 g.) in ethanol (20 ml.) was hydrogenated with 30% palladium-charcoal (0.025 g.) as catalyst. One molar equivalent of hydrogen was taken up and then absorption ceased. The reaction mixture was filtered free of catalyst and taken to dryness on the steam-bath. The crude product was crystallized from methanol giving dihydro- γ -metasantonin as small, white needles, m.p. 186–188° (lit.^{10,11} 180°, 181–182°), yield 0.20 g. (79%); infrared spectrum (CHCl_3), bands at 5.71 and 5.84 μ ; ultraviolet spectrum (95% EtOH), λ_{max} 219 $\text{m}\mu$ ($\log \epsilon$ 4.19) and 287 $\text{m}\mu$ ($\log \epsilon$ 1.33).

Action of Base on Dihydro- γ -metasantonin: Formation of the Diketo Ester X.—Dihydro- γ -metasantonin (1.35 g.) was heated on the steam-bath with aqueous 8% sodium hydroxide (10 ml.) for 2 hours; the solid completely dissolved to give a yellow solution with a greenish fluorescence. The solution was cooled, acidified with 12 *N* sulfuric acid and extracted with ether. The

etheral extract was shaken with aqueous sodium bicarbonate and the aqueous solution was acidified and extracted with ether. This etheral extract was dried over anhydrous magnesium sulfate and evaporated to small bulk when 0.12 g. of white crystalline material was deposited.²⁰ Removal of the ether from the mother liquor gave the major product as a sirup. Esterification of this product with etheral diazomethane followed by concentration of the etheral solution gave white prisms, m.p. 180–186°. Recrystallization from ether raised the m.p. to 185.5–187.5°; infrared spectrum (CHCl_3), bands at 5.78 and 5.82 μ .

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_4$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.71.

α -Tetrahydrosantonin (XI).—Santonin (4.0 g.) in ethanol (125 ml.) was hydrogenated with 30% palladium-charcoal (0.25 g.) as catalyst. The absorption of hydrogen stopped after the uptake of 2.1 molar equivalents. After removal of catalyst by filtration, the solution was evaporated to very small bulk, when cooling in an ice-bath gave 2.3 g. of a mixture of isomeric tetrahydrosantonins, m.p. 130–145°. Two recrystallizations from 50% aqueous ethanol gave α -tetrahydrosantonin as white, glistening leaflets, m.p. 154–155° (lit.¹⁸ 155–156°), yield 1.60 g. (39%); infrared spectrum (CHCl_3), bands at 5.65 and 5.84 μ ; ultraviolet spectrum (95% EtOH), λ_{max} 286 $\text{m}\mu$ ($\log \epsilon$ 1.28).

Conversion of α -Tetrahydrosantonin to the Diketo Ester X.— α -Tetrahydrosantonin (1.55 g.) was heated on the steam-bath with aqueous 8% sodium hydroxide (10 ml.) for 0.5 hour. The pale yellow solution was cooled, made slightly acid with 3 *N* sulfuric acid and extracted with ether. The cooled etheral extract was immediately treated with a slight excess of diazomethane; evaporation gave crude methyl tetrahydrosantoninate as a sirup. The sirup was taken up in acetic acid (20 ml.) and treated at 40° with a solution of chromium trioxide (0.80 g.) in acetic acid (10 ml.) and water (0.5 ml.) added dropwise with shaking over a period of 15 minutes.

The mixture was left to stand for 24 hours, diluted with water (30 ml.) and treated with a few drops of aqueous sodium bisulfite to remove excess chromium trioxide. It was boiled vigorously to remove most of the acetic acid, water being added from time to time to maintain the volume approximately constant. The solution was cooled and extracted with ether. The etheral extract was shaken with aqueous sodium bicarbonate, separated from the aqueous layer and freed of ether on the steam-bath. The residual sirup was boiled with excess aqueous ethanolic potassium hydroxide for 0.5 hour. The solution was diluted with water, acidified with 3 *N* sulfuric acid and extracted with ether. The etheral extract was treated with excess diazomethane and the crude methyl ester obtained as a sirup by removal of the ether. This was dissolved in benzene and chromatographed on alumina (15 \times 1.5 cm.); elution with benzene gave a solid, which on recrystallization from ether gave the product as white prisms, m.p. 186–188°, undepressed by admixture with the material, m.p. 185.5–187.5°, obtained by the action of base on γ -metasantonin. The infrared spectra of these two products were identical.

(20) This product, m.p. 136–140°, gave a methyl ester with etheral diazomethane, m.p. 116–119°; infrared spectrum (CHCl_3), composite band at 5.78–5.82 μ . The latter may correspond to the dimethyl β_2 -3,6-dioxo-eudesmanoate of Banerji, Barton and Cookson.¹⁹

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

The Structure of the α - and β -Metasantonins¹

By R. B. WOODWARD AND PETER YATES

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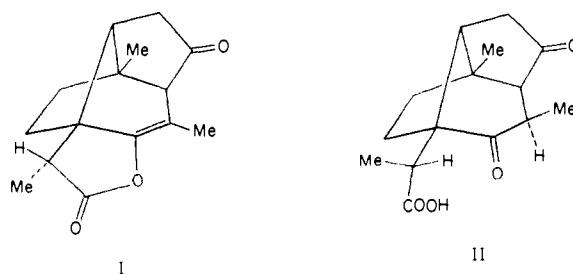
α - and β -Metasantonin, the products of the action of concentrated sulfuric acid on parasantonide or parasantonin acid, are shown to have the structures XIII and XII, respectively.

Parasantonide, $\text{C}_{15}\text{H}_{18}\text{O}_3$, one of the two stereoisomeric products formed by treatment of santonin acid with acetic acid followed by pyrolysis has been shown to possess the structure I.^{2,3} Treatment of parasantonide or the corresponding acid, parasantonin acid (II), with

(1) Presented in the course of a series of lectures at University College, London, in April–May, 1951.

(2) R. B. Woodward and E. G. Kovach, *J. Am. Chem. Soc.*, **72**, 1009 (1950).

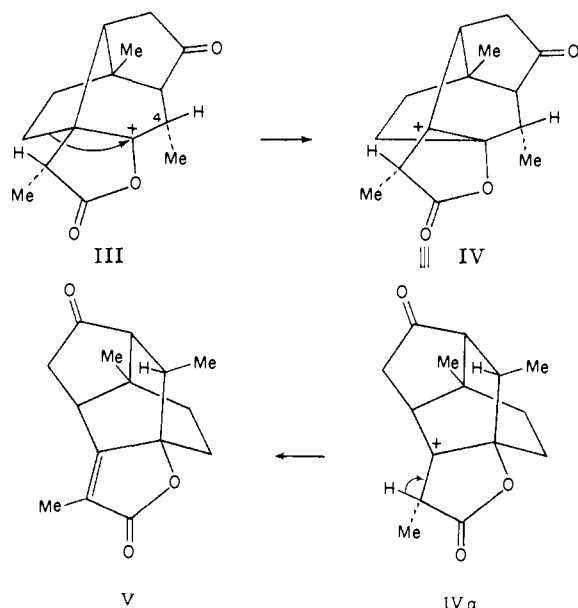
(3) R. B. Woodward and P. Yates, *Chemistry and Industry*, 1391 (1954); see also footnotes 3 and 4 in reference 6.



either boiling hydriodic acid and phosphorus or with warm concentrated sulfuric acid gives a mixture of two new isomers of parasantonide, the α - and β -metasantonins.^{4,5} These substances are also isomeric with γ -metasantonin, the product obtained by the action of warm concentrated sulfuric acid on santonic acid.⁶ We now discuss the elucidation of the structure of α - and of β -metasantonin.

Examination of the infrared and ultraviolet spectra of β -metasantonin gives important information concerning the functional groups present in the molecule. A strong band at 5.75μ accompanied by a weak band at 5.92μ is reminiscent of the spectra of α, β -unsaturated butyrolactones, e.g., the lactone of 2-(2-hydroxycyclohexylidene)-propionic acid,⁷ iresin⁷ and isoiresin.⁸ Furthermore, the high intensity absorption maximum exhibited by β -metasantonin in the ultraviolet at $226 m\mu$ also bespeaks the presence of a lactone system with a heavily substituted double bond in conjugation with the carbonyl group.^{7,9} The functionality of the third oxygen atom may also be deduced from the spectral data. The presence of a low intensity maximum in the ultraviolet at $298 m\mu$ indicates the presence of an isolated carbonyl function. That this is present as a ketonic carbonyl group in a five-membered cycle is evident from the infrared spectrum which shows only a single carbonyl stretching band (5.75μ), which must represent the overlap of the band associated with the conjugated lactone system with that of a cyclopentanone carbonyl group.

Armed with these deductions we were led to the view that the structure V is the most probable representation for β -metasantonin. It is apparent that such a compound could arise from parasantonide by a series of acid-catalyzed changes ($I \rightarrow III \rightarrow IV \rightarrow V$, arrows) having prototypes of impeccable authenticity.¹⁰ That such a formulation for β -metasantonin is correct was



demonstrated by degradative methods.

(4) S. Cannizzaro and G. Carnelutti, *Gazz. chim. ital.*, **10**, 461 (1880).

(5) The α - and β -metasantonin are also formed by the action of boiling hydriodic acid and phosphorus on santonic acid: S. Cannizzaro and D. Amato, *Gazz. chim. ital.*, **4**, 446 (1874); *Ber.*, **7**, 1103 (1874); S. Cannizzaro and G. Carnelutti, *Gazz. chim. ital.*, **8**, 318 (1878). It is most probable that this reaction proceeds via the prior formation of parasantonide.

(6) R. B. Woodward and P. Yates, *J. Am. Chem. Soc.*, **85**, 551 (1963).

(7) C. Djerassi, P. Sengupta, J. Herran and F. Walls, *ibid.*, **76**, 2966 (1954); C. Djerassi and S. Burstein, *Tetrahedron*, **7**, 37 (1959).

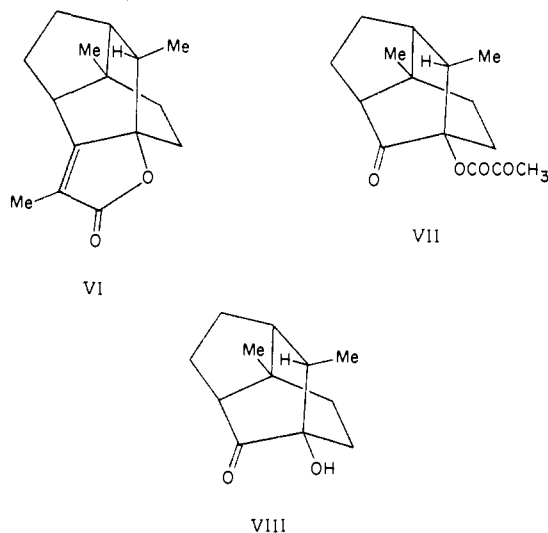
(8) P. Crabbe, S. Burstein and C. Djerassi, *Bull. soc. chim. Belges*, **67**, 632 (1958).

(9) A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957).

(10) It is not implied that two or more of these steps may not be concerted.

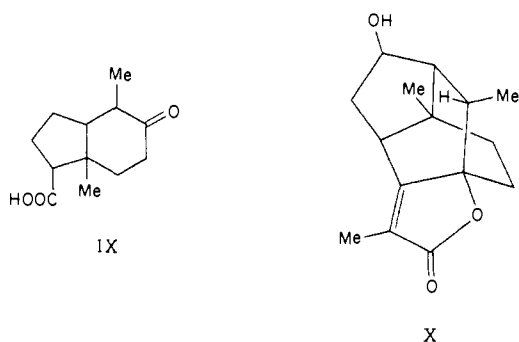
Reduction of β -metasantonin by the Wolff-Kishner method gave deoxo- β -metasantonin, $C_{16}H_{20}O_2$, which shows bands at 5.77 and 5.93μ in its infrared spectrum, corresponding to an α, β -unsaturated butyrolactone, but with the relative intensity of the 5.77μ band reduced in comparison with the corresponding band at 5.75μ in β -metasantonin. In addition, the ultraviolet spectrum of the deoxo derivative, while retaining a high intensity maximum in the low wave length region, no longer shows the low intensity maximum at $298 m\mu$ present in the spectrum of β -metasantonin which has been attributed to the presence of an isolated carbonyl group. Thus VI is a satisfactory representation of deoxo- β -metasantonin.

Ozonolysis of deoxo- β -metasantonin in ethyl acetate, followed by decomposition of the ozonide with water and basic hydrolysis of the crude reaction product, gave a compound, $C_{12}H_{18}O_2$, which we designate β -metasantonol, and pyruvic acid, identified as its *p*-nitrophenylhydrazone. The infrared spectrum of β -metasantonol shows bands at 2.93 and 5.83μ , indicating the presence of a hydroxyl group and of a saturated carbonyl group present in an acyclic or a six-membered ring system. Significantly, the weak band at 5.92 – 5.93μ present in the spectra of β -metasantonin and deoxo- β -metasantonin is absent from that of β -metasantonol, showing that rupture of the unsaturated lactone ring has occurred. Further, the ultraviolet spectrum of β -metasantonol shows a single, low intensity maximum at $288 m\mu$, confirming the presence of an isolated carbonyl function and the absence of the conjugated lactone function. The structure VIII gives, therefore, an accurate representation of the properties of β -metasantonol, which may be considered to arise by hydrolysis of the pyruvate ester VII, formed by normal ozonolytic cleavage of the double bond of VI.



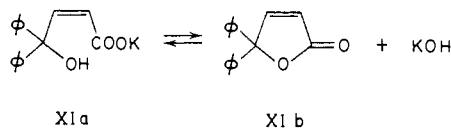
The presence of the α -ketol function in β -metasantonol (VIII) was confirmed by its reaction with sodium periodate, when it was oxidized to a keto acid, $C_{12}H_{18}O_3$, which behaved as a monobasic acid on titration. The infrared spectrum of the acid shows the characteristic features of a carboxylic acid, with a broad band in the 3μ region and a strong carbonyl band at 5.85μ , which could arise from the overlap of bands associated with a carboxylic acid function and a six-membered cyclic ketone. The ultraviolet spectrum, with a low intensity maximum at $286 m\mu$, confirms the presence of an isolated ketone group. The keto acid may hence be formulated as a 3a,4,5,6,7,7a-hexahydro-4,7a-dimethyl-5-oxo-indan-1-carboxylic acid (IX).¹¹ This series of

(11) The absence of a lower wave length carbonyl band in the infrared spectrum of the keto acid serves to eliminate the possibility of migration



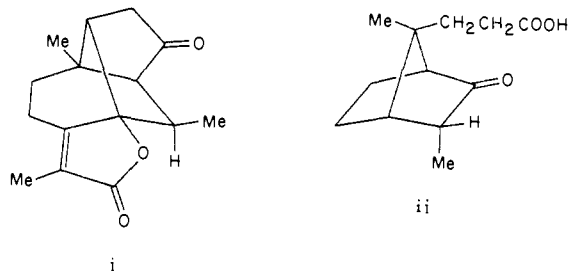
transformations serves to confirm the designation of V as the structure of β -metasantonin.

Some comment must be made concerning the remarkable resistance of β -metasantonin to hydrolysis, especially under basic conditions. After treatment with boiling 50% aqueous potassium hydroxide, β -metasantonin was recovered unchanged and could in fact be largely extracted with ether directly from the basic reaction mixture. Treatment with boiling ethanolic potassium hydroxide converted β -metasantonin to a dihydro- β -metasantonin, $C_{15}H_{20}O_3$; that the lactone ring remained intact in this product, however, was indicated by the persistence of bands at 5.77(s) and 5.93(w) μ in its infrared spectrum. The reduction of the relative intensity of the carbonyl stretching band and the appearance of a weak band at 2.96 μ demonstrated that the new product had been formed by reduction of the ketonic carbonyl group of V to give X. Such a reduction of a carbonyl group with ethanolic base is of a type which has ample precedent.¹² Thus the lactone ring of V defies hydrolytic fission completely under the most vigorous of conditions. This remarkable behavior of a heavily substituted butyrolactone system is not without analogy. For example, the basicity of an aqueous solution of the potassium salt XIa slowly increases on standing and the lactone XIb is deposited from the solution.^{13,14} These phenomena exemplify



the fact that the equilibria between the open and closed forms of such systems lie heavily in favor of the closed forms.¹⁵

of the alternative available bond in a cation epimeric with III at C.4, which would lead to structure i for metasantonin and ii for the derived keto acid. Confirmation of this conclusion was obtained from the infrared spectrum of the methyl ester of the keto acid which had bands at 5.79 μ (ester) and 5.83 μ (six-membered cyclic ketone).



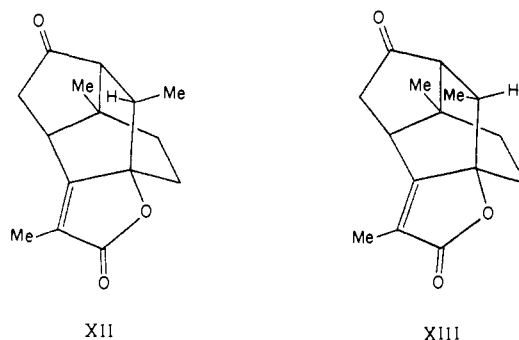
(12) Cf. R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); W. von E. Doering, G. Coates and L. H. Knox, *ibid.*, **69**, 1700 (1947); W. von E. Doering and T. C. Aschner, *ibid.*, **75**, 393 (1953).

(13) H. Stobbe, *Ann.*, **308**, 89 (1899).

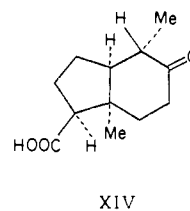
(14) Cf. R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **72**, 399 (1950).

(15) It is to be noted that in the case of α,β -unsaturated lactones these considerations apply only if the hydroxyl group is tertiary, as in V. Otherwise, ketonization of the open unsaturated alcohol will drive the equilibrium over to the open form; cf. the basic hydrolysis of γ -metasantonin.⁸

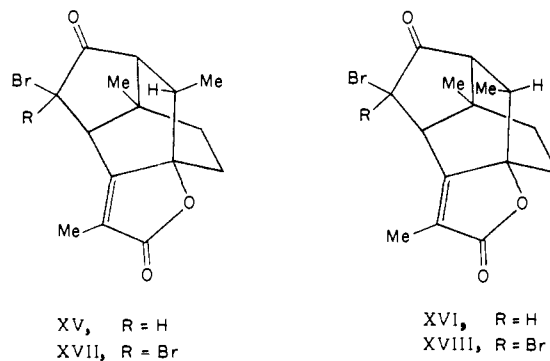
The close similarity of the infrared and ultraviolet spectra of α -metasantonin and β -metasantonin suggests strongly that these two compounds are stereoisomeric, though no positive chemical evidence is available which excludes the possibility that the former has the structure i.¹¹ The rigid, tetracyclic system of V allows the existence of only two stereoisomeric forms of this structure with absolute configuration related to santonin: these are XII (\equiv V) and XIII, which must therefore represent the isomeric lactones. Further,



we have found that β -metasantonin will form a 2,4-dinitrophenylhydrazone under the usual conditions, while α -metasantonin fails to do so; the structure XII in which the ketonic carbonyl group is less hindered may therefore be assigned to β -metasantonin, and XIII to α -metasantonin. It follows that the keto acid IX most probably has the configuration shown in XIV.



Next must be considered the products of bromination of α - and β -metasantonin reported by Cannizzaro and Carnelutti.^{4,5} Each compound gave a monobromo derivative on treatment with one molar equivalent of bromine in chloroform. Bromination with excess bromine gave in each case a dibromo derivative. These bromine derivatives are readily formulated on the basis of structures XII and XIII as XV-XVIII; moreover, the introduction of only two bromine atoms

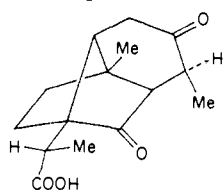


when excess of bromine is used is in accord with the structural assignments, in that no further substitution by bromine would be expected to occur since this would require enolization toward the bridgeheads of small atom-bridged ring systems.¹⁶

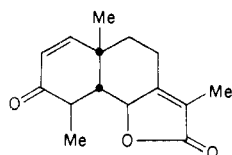
It remains only to discuss the sharp contrast in the behavior of santonic acid (XIX \rightarrow XX) on the one

(16) Addition of bromine to the fully substituted, conjugated double bond of XII or XIII would not be anticipated; cf. W. Cocker and S. Hornsby, *J. Chem. Soc.*, 1157 (1947).

hand, and parasantonin acid (XXI \rightarrow XXII) on the

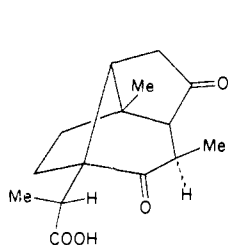


XIX

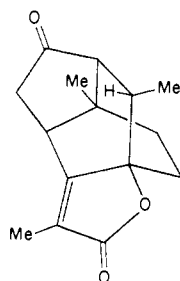


XX

other, when each of these acids is treated with warm



XXI (= II)



XXII (= XII)

sulfuric acid under the same conditions.⁶ The relative dispositions of reactive groupings in the two molecules are very similar, and the electronic path followed in the decomposition of either acid should *a priori* be available to the other. Consequently, the divergent fates of the two substances must be associated with relatively subtle stereoelectronic factors, or with the presence of substantially different skeletal arrangements in the acids. It is not unreasonable to suppose that the relatively high degree of strain¹⁷ in the bicyclo[2.2.1]-heptane skeleton of XIX favors the observed ring cleavage in that case. Further, the cleavage reaction must be preceded by enolization of the appropriate carbonyl system, and that process may be expected to be considerably more difficult for the cyclopentanone XXI than for the cyclohexanone XIX.¹⁸

Experimental

α - and β -Metasantonin (XIII and XII).⁴—Parasantonin acid² (7.5 g.) was heated on the steam-bath with concentrated sulfuric acid (50 ml.) for 3 hours. The black solution was cooled and added with stirring to cold water (2 l.). The mixture was made slightly basic by the addition of solid sodium carbonate and extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and concentrated until crystallization commenced. The yield (two crops) of the mixture of α - and β -metasantonins was 5.5 g. (80%). The mixture was dissolved in the minimum volume of boiling ether and allowed to evaporate slowly at room temperature over a period of several days. When very little solvent remained, the crystals were carefully filtered, washed with a little ether and separated by hand-picking. The α -metasantonin (2.0 g.) crystallized as laminae, the β -metasantonin as large prisms (3.4 g.). Two recrystallizations of the crude α -metasantonin from ether gave the pure isomer; yield, 1.85 g. (27%). Recrystallization of the crude β -metasantonin from ether gave the pure isomer; yield 3.12 g. (45%).

β -Metasantonin 2,4-Dinitrophenylhydrazone.— β -Metasantonin dissolved in ethanol was treated with a solution of 2,4-dinitrophenylhydrazine in aqueous ethanolic sulfuric acid in the usual manner.¹⁹ The orange deposit formed after the mixture had stood for 12 hours at room temperature was filtered and twice crystallized from ethanol to give the hydrazone as an orange solid, m.p. 270–272° dec.

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: N, 13.14. Found: N, 12.68.

Similar treatment of α -metasantonin gave no precipitate; concentration of the solution yielded only unreacted α -metasantonin.

Attempted Hydrogenation of β -Metasantonin.— β -Metasantonin (0.20 g.) in ethanol (20 ml.) was stirred with palladium (prepared by pre-reduction of 0.020 g. of palladium oxide) in an at-

| | M. p., °C. | Ultraviolet spectrum (EtOH) λ_{max} , m μ (log ϵ) | Infrared spectrum (CHCl ₃), μ |
|------------------------|--|---|---|
| α -Metasantonin | 159–160.5 (lit. ⁴ 160.5) | 226 (4.03) | 5.76 (s) |
| β -Metasantonin | 135.5–137 (lit. ⁴ 136) | 305 (1.87) 226 (4.03) 298 (1.80) | 5.93 (w) 5.75 (s) 5.92 (w) |

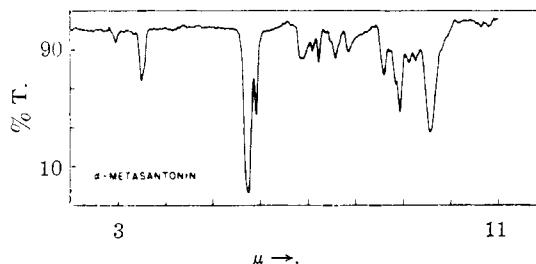


Figure 1.

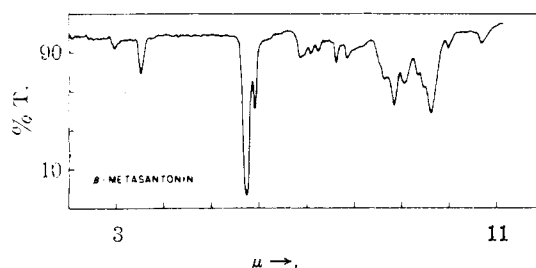


Figure 2.

mosphere of hydrogen. No absorption of hydrogen occurred during the course of one half-hour. Platinum oxide (0.020 g.) was then added to the mixture; 5 ml. of hydrogen was absorbed rapidly (this corresponded with the volume of hydrogen required to reduce the catalyst as determined in a blank run) but there was no further absorption during the course of an additional half-hour.

Attempted Hydrolysis of β -Metasantonin.—(i) β -Metasantonin (0.20 g.) and aqueous 20% potassium hydroxide (10 ml.) were heated on the steam-bath for 5 hours. Only partial solution of the solid occurred, giving a yellow solution. The mixture was boiled for 1 hour but solution was far from complete. Solid potassium hydroxide was added to increase the concentration to 50% and the mixture was boiled for a further 2 hours; no more solid appeared to go into solution. Extraction with ether yielded unreacted β -metasantonin (0.15 g.), m.p. 134.5–137°. Acidification and ethereal extraction of the aqueous base gave slightly impure β -metasantonin (0.023 g.). (ii) β -Metasantonin (0.25 g.) and 10% sulfuric acid (10 ml.) were boiled under reflux for 12 hours; a turbid solution resulted. When the solution was cooled, β -metasantonin (0.205 g.), m.p. 135–136°, was recovered. Extraction of the mother liquor with ether yielded only further β -metasantonin (0.025 g.), m.p. 130–133°.

Dihydro- β -metasantonin (X).— β -Metasantonin (0.15 g.), potassium hydroxide (4.0 g.) and ethanol (9 ml.) were boiled under reflux for 12 hours. The hot solution was poured into a large excess of cold water and the resulting solution was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and freed of solvent giving a pale yellow solid (0.12 g.). Two recrystallizations from ether gave dihydro- β -metasantonin as hard, white prisms, m.p. 152–153°; infrared spectrum (CHCl₃), bands at 2.96(w), 5.77(s), 5.93(w) μ ; ultraviolet spectrum (EtOH), λ_{max} 224 m μ (log ϵ 4.13).

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 72.55; H, 8.12. Found: C, 72.70; H, 8.14.

Deoxo- β -metasantonin (VI).— β -Metasantonin (2.0 g.), 85% hydrazine hydrate (2.0 ml.), potassium hydroxide (2.0 g.) and triethylene glycol (10 ml.) were boiled under reflux for 2.5 hours. The condenser was removed and the bath temperature slowly raised until all the water had boiled away from the reaction mixture, as indicated by the cessation of frothing. The condenser was replaced and the mixture maintained at 195–205° for 4 hours. It was cooled, diluted with water (15 ml.) and extracted

(17) Cf. P. von R. Schleyer, *J. Am. Chem. Soc.*, **80**, 1700 (1958).

(18) Cf. G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 669 (1947); G. Schwarzenbach, M. Zimmermann and V. Prelog, *ibid.*, **34**, 1954 (1951).

(19) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

with ether. The ethereal extract was dried over anhydrous magnesium sulfate and, after removal of solvent, gave the crude product as an oil. This was dissolved in benzene (20 ml.) and chromatographed on an alumina column (16 × 1.5 cm., packed in benzene). The column was eluted with benzene; the first 20-ml. cut yielded a mixture of solid and oil and was discarded; the subsequent 120 ml. of benzene eluted 1.37 g. (73%) of solid material, m.p. 53–54°. Purification was effected by sublimation at 100–110° (1 mm.) giving deoxo- β -metasantonin as a white solid, m.p. 54–55°; infrared spectrum (CHCl₃), bands at 5.77(s), 5.93(w) μ ; ultraviolet spectrum (EtOH), λ_{\max} 224 m μ (log ϵ 4.15).

Anal. Calcd. for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found: C, 78.07; H, 8.93.

β -Metasantonol (VIII).—Deoxo- β -metasantonin (0.50 g.) in ethyl acetate (20 ml.) was treated with excess of ozone at the temperature of an ice-salt-bath. Dissolved ozone was blown from the solution by a current of nitrogen. The solution was treated with water (15 ml.) and cautiously warmed to 50° while ethyl acetate was evaporated by means of a water aspirator. Ether and aqueous sodium bicarbonate were added and the mixture shaken and separated. The ethereal layer was dried over anhydrous sodium sulfate and gave, after removal of the solvent, a colorless oil (0.6 g.). This was dissolved in 95% ethanol (2 ml.) and a solution of potassium hydroxide (0.25 g.) in water (5 ml.) added; the mixture was boiled under reflux for 1 hour. The solution was cooled, diluted with an equal volume of water and extracted with ether. The aqueous layer was heated on the steam-bath to remove most of the ethanol and acidified with acetic acid. To the solution was added a solution of *p*-nitrophenylhydrazine in glacial acetic acid; an orange precipitate was formed immediately. This was recrystallized from aqueous ethanol giving an orange solid, m.p. 214–216°

dec.; mixed with pyruvic acid *p*-nitrophenylhydrazone, m.p. 215–217° dec. The ethereal layer from the hydrolysis reaction was dried over anhydrous sodium sulfate and freed of solvent giving a sticky, white, very volatile solid. This was sublimed at 100–110° (760 mm.) and the sublimate (0.32 g.) taken up in benzene (5 ml.) and chromatographed on alumina (12 × 1.5 cm., packed in benzene). The following eluents were used: benzene (100 ml.), 50% ether–50% benzene (100 ml.) and ether (150 ml.); 25-ml. cuts were taken. Fractions 4–12, which contained white solid, were recombined to give a white solid, m.p. 90–95°, yield 0.23 g. (55%). Two sublimations at 100–110° (760 mm.) gave pure β -metasantonol, m.p. 95–96°; infrared spectrum (CHCl₃), bands at 2.93(w), 5.83(s) μ ; ultraviolet spectrum (EtOH), 288 m μ (log ϵ 1.47).

Anal. Calcd. for C₁₅H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.84; H, 9.48.

3a,4,5,6,7,7a-Hexahydro-4,7a-dimethyl-5-oxo-indan-1-carboxylic Acid (XIV).— β -Metasantonol (0.065 g.) was shaken vigorously with 0.21 *M* aqueous sodium periodate (20 ml.) until solution was effected. After standing at room temperature for 20 hours the solution was extracted with ether and the ethereal extract was then extracted with aqueous sodium bicarbonate. The bicarbonate extract was acidified with 6 *N* sulfuric acid and extracted with ether. This ethereal extract was dried over anhydrous sodium sulfate and gave, after removal of ether, the crude keto acid as a colorless oil. Trituration of the oil with a little benzene gave a white solid, m.p. 120–123°; yield 0.065 g. (95%). Two recrystallizations from benzene–ether gave white prisms, m.p. 125–127°; infrared spectrum (CHCl₃), bands at 2.9–3.4, 5.85(s,b) μ ; ultraviolet spectrum (EtOH), λ_{\max} 286 m μ (log ϵ 1.54).

Anal. Calcd. for C₁₅H₁₈O₃: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.61.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

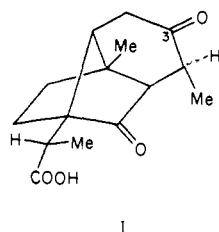
The Structure of Tribromosantonin¹

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Tribromosantonin, the product of the action of bromine on santonin acid, is shown to have the structure V.

The deduction of the structure I for santonin acid² has been followed^{3–5} by the elucidation of the structures



of all but one of the known transformation products of this compound. In the present report we discuss the structure of the remaining product, tribromosantonin.

Tribromosantonin was obtained by Francesconi⁶ by the action of excess bromine on santonin acid dissolved in "wet chloroform." It was assigned the formula C₁₅H₁₅O₃Br₃, and was found to be insoluble in aqueous sodium carbonate. Repetition of Francesconi's procedure gave variable yields of tribromosantonin, averaging 12%. It was observed that the reaction was subject to a considerable period of induction. The procedure was therefore modified by the addition of a small amount of 40% hydrobromic acid

to the reaction mixture; this resulted in a reduction of the induction period and the formation of tribromosantonin in somewhat increased, but still not entirely reproducible, yields. It was subsequently found that the use of glacial acetic acid as solvent led to higher and reproducible yields; the identity of the products prepared by the different procedures was shown by infrared spectral comparisons and mixture melting points.⁷ Elemental analysis of the product from the reaction in wet chloroform gave results which were more concordant with an empirical formula C₁₅H₁₆O₄Br₃ than with the formula C₁₅H₁₅O₃Br₃ proposed by Francesconi, although a satisfactory bromine analysis was not obtained for this product. That tribromosantonin indeed possesses the formula C₁₅H₁₅O₃Br₃ was shown by elemental analysis of the product prepared in acetic acid for which analytical figures were obtained in excellent agreement with calculated values for this formula, but at considerable variance with those calculated for C₁₅H₁₆O₄Br₃.

The infrared spectrum of tribromosantonin shows three bands in the 5–6 μ region at 5.45, 5.66 and 5.86 μ , and a weak band at 6.12 μ . The pair of bands at lowest wave lengths is characteristic of a five-membered cyclic anhydride,⁸ the band at 5.86 μ may be assigned to a third carbonyl group, and that at 6.12 μ to an ethylenic double bond. Thus the infrared spectrum permits the assignment of the functionality of all four oxygen atoms of tribromosantonin. Its ultraviolet

(7) Francesconi⁶ gives m.p. 187–188° for tribromosantonin; we find that it melts with decomposition at a temperature which is very dependent upon the temperature to which the heating bath is pre-heated. When the bath was pre-heated to 180°, the observed m.p. (capillary) was 195–200° dec.

(8) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953).

(1) Based, in large part, on the Ph.D. Thesis of S. G. Levine, Harvard University, 1953.

(2) R. B. Woodward, F. J. Brutschy and H. Baer, *J. Am. Chem. Soc.*, **70**, 4216 (1948); for discussion of configuration, see R. B. Woodward and P. Yates, *Chem. Ind. (London)*, 1391 (1954), and footnotes 3 and 4 in ref. 4.

(3) R. B. Woodward and E. G. Kovach, *J. Am. Chem. Soc.*, **72**, 1009 (1950).

(4) R. B. Woodward and P. Yates, *ibid.*, **85**, 551 (1963).

(5) R. B. Woodward and P. Yates, *ibid.*, **85**, 553 (1963).

(6) L. Francesconi, *Gazz. chim. ital.*, **29**ii, 256 (1899).