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 ($CHCl_3$), bands at 5.77(s), 5.93(w) μ; ultraviolet spectrum (EtOH), $\lambda_{max}$ 224 mμ (log ε 4.15).

*Anal.* Calcd. for $C_{15}H_{20}O_2$: 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 ($CHCl_3$), bands at 2.93(w), 5.83(s) μ; ultraviolet spectrum (EtOH), 288 mμ (log ε 1.47).

*Anal.* Calcd. for $C_{12}H_{18}O_2$: 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 benzin gave a white solid, m.p. 120–123°; yield 0.065 g. (95%). Two recrystallizations from benzin–ether gave white prisms, m.p. 125–127°; infrared spectrum ($CHCl_3$), bands at 2.9–3.4, 5.85(s,b) μ; ultraviolet spectrum (EtOH), $\lambda_{max}$ 286 mμ (log ε 1.54).

*Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.76; H, 8.61.

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

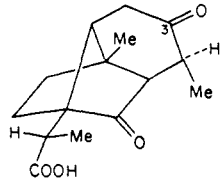
# The Structure of Tribromosantonin[1]

BY R. B. WOODWARD, S. G. LEVINE AND PETER YATES

RECEIVED JULY 30, 1962

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

The deduction of the structure I for santonic acid[2] has been followed[3–5] by the elucidation of the structures




I

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 Francesconi[6] by the action of excess bromine on santonic acid dissolved in "wet chloroform." It was assigned the formula $C_{15}H_{15}O_3Br_3$, 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 $C_{15}H_{15}O_4Br_3$ than with the formula $C_{15}H_{15}O_3Br_3$ proposed by Francesconi, although a satisfactory bromine analysis was not obtained for this product. That tribromosantonin indeed possesses the formula $C_{15}H_{15}O_4Br_3$ 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 $C_{15}H_{15}O_3Br_3$.

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

(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.*, **29ii**, 256 (1899).

(7) Francesconi[6] 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.

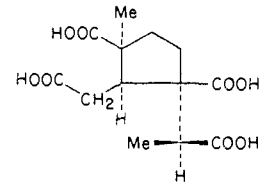
(8) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953).

spectrum shows maxima at 246 mμ (log ε 3.72) and 323 mμ (log ε 2.26) with high intensity end absorption. This spectrum clearly indicates that the third carbonyl group is conjugated with the double bond.

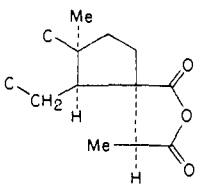
In order to confirm the presence of a cyclic anhydride system, tribromosantonin was subjected to a variety of hydrolytic conditions. All of these reactions led to intractable, acidic gums which resisted purification. It appeared probable that the presence of several bromine atoms in tribromosantonin was the cause of the complexity of the hydrolytic reaction products. Attention was therefore directed to the removal of the bromine atoms by means of a selective reagent which would not effect reduction elsewhere in the molecule. The reagent chosen for this purpose was chromous chloride.[9]

Treatment of tribromosantonin with an excess of 0.75 *M* ethanolic chromous chloride led to the formation of a bromine-free, acidic gum (II) which failed to crystallize. This product had bands at 2.9–3.5, 5.79 and 6.00 μ in its infrared spectrum and a high intensity maximum at 238 mμ in its ultraviolet spectrum, indicating the presence of carboxylic acid and α,β-unsaturated ketonic functions. By vacuum sublimation of II **a crystalline, neutral compound, III, $C_{15}H_{18}O_4$,** was obtained; this product could also be obtained directly from tribromosantonin in much higher yield by reduction with zinc in acetic anhydride and ethyl acetate. Compound III had bands at 5.45, 5.65 and 5.98 μ in its infrared spectrum and maxima in its ultraviolet spectrum at 237 mμ (log ε 4.00) and 323 mμ (log ε 1.61). The presence of the bands at 5.45 and 5.65 μ shows that the five-membered cyclic anhydride present in tribromosantonin is also present in III. The relationship between II and III is clearly that between a succinic acid and its anhydride. This was confirmed by the observation that when the neutral compound III was warmed with aqueous sodium bicarbonate it was converted to a crystalline acid whose infrared spectrum was very similar to that of II. The presence of an α,β-unsaturated ketonic group in III is indicated by the band at 5.98 μ in its infrared spectrum and corroborated by the positions and intensities of the maxima in its ultraviolet spectrum. The position of the high intensity maximum in the latter spectrum further indicates that the conjugated double bond is disubstituted.[10] Catalytic hydrogenation of III proceeded with the uptake of one molar equivalent of hydrogen and the formation of a product with infrared bands at 5.45, 5.64 and 5.83 μ which evidently results from saturation of the conjugated double bond in III.

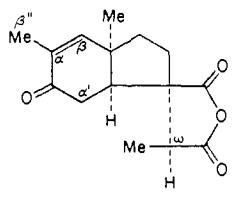
From the consideration of the functional groups we now turned to the elucidation of the skeletal features of compound III. Ozonolysis at −80° followed by treatment with dilute aqueous hydrogen peroxide gave α-santoric acid (IV),[2] identified by infrared spectral comparison and mixture melting point with an authentic sample prepared by oxidation of santonic acid.[11] This tetracarboxylic acid retains all but two of the fifteen carbon atoms of III and thus is of decisive importance in establishing its skeleton; moreover, since only two of the four carboxylic acid functions of α-santoric acid are in a vicinal relationship, it must be these which are involved in the cyclic anhydride system of III. The partial structure IIIa is thus established. On the basis of the evidence already discussed, this can be expanded in only two ways to provide possible full structures for III, *i.e.*, IIIb (≡ IIId) and IIIc (≡ IIIe). Comparison of these with the structure of santonic acid (I) leads to the exclusion of IIIc on the grounds of the improbability that C.3 should be reduced from a ketone to a methine group during the course of the observed transformations; compound III is therefore formulated as IIIb (≡ IIId).



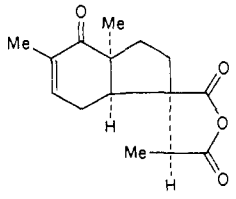

IV



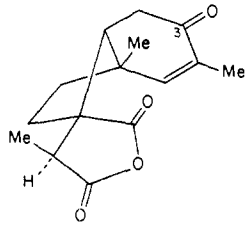

III a



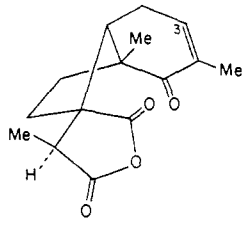

III b




III c




III d




III e

Since IIIb is formed from tribromosantonin under mild reductive conditions and the infrared and ultraviolet spectra of these compounds show that they contain the same carbonyl functions, it may be concluded that their skeletons are the same and that the structure of tribromosantonin is related to IIIb by the substitution of three bromine for three hydrogen atoms. The sites of the bromine atoms must be such, of course, that their removal by chromous chloride or zinc and acetic anhydride is possible. One such site is the β-carbon atom of the α,β-unsaturated ketonic system. The position of the high intensity band (246 mμ) in the ultraviolet spectrum of tribromosantonin, however, contraindicates the presence of a bromine atom on this carbon. For, although data on such systems are sparse, the evidence available[12] suggests that the bathochromic shift resulting from the introduction of a β-bromine atom onto an α,β-unsaturated ketonic system is *ca.* 30 mμ, and thus a 3-bromo-2-methyl-2-cyclohexen-1-one system would be expected to have its high intensity ultraviolet maximum at 265 ± 5 mμ [any shift due to the presence of bromine atoms on the α'-carbon atom would be anticipated to be bathochromic (*vide infra*)]. Decisive evidence against the presence of a bromine atom on the ethylenic system of tribromosantonin was forthcoming from its nuclear magnetic resonance spectrum ($CDCl_3$), which shows a peak at $\tau$ = 3.34 p.p.m., characteristic of a hydrogen atom on an ethylenic double bond attached to a strongly electron-withdrawing group.[13] This spectrum also permits the exclusion of another possible site for a bromine atom—the carbon atom designated as ω in

(9) *Cf.* P. L. Julian, W. Cole, A. Magnani and E. W. Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945); C. Djerassi and C. R. Scholz, *ibid.*, **69**, 2404 (1947).

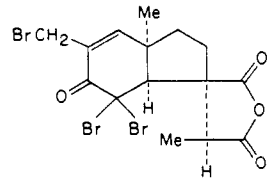
(10) R. B. Woodward, *ibid.*, **63**, 1123 (1941); **64**, 76 (1942).

(11) L. Francesconi, *Gazz. chim. ital.*, **22i**, 181 (1892).

(12) K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(13) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 61.

IIIb—on the basis of an examination of the peaks associated with the methyl groups. The spectrum shows the presence of *two methyl groups*, one giving rise to a singlet with $\tau = 8.30$ p.p.m. and the other to a doublet centered at $\tau = 8.33$ p.p.m. with $J = 7$ c.p.s. The former can be assigned to an angular methyl group and the latter to a methyl group attached to the $\omega$-carbon atom as in IIIb[14]; the $\omega$-carbon atom therefore bears a hydrogen atom in tribromosantonin, and cannot be the site of a bromine atom. The only remaining sites for the bromine atoms are the $\alpha'$-and $\beta''$-carbon atoms; the presence of bromine on the $\beta''$-carbon atom is also evidenced by the lack of a third methyl peak in the nuclear magnetic resonance spectrum of tribromosantonin. Of the structures based on IIIb with three bromine atoms on the $\alpha'$- and $\beta''$-carbon atoms, only V is compatible with the full nuclear magnetic resonance spectrum of tribromosantonin. A quartet

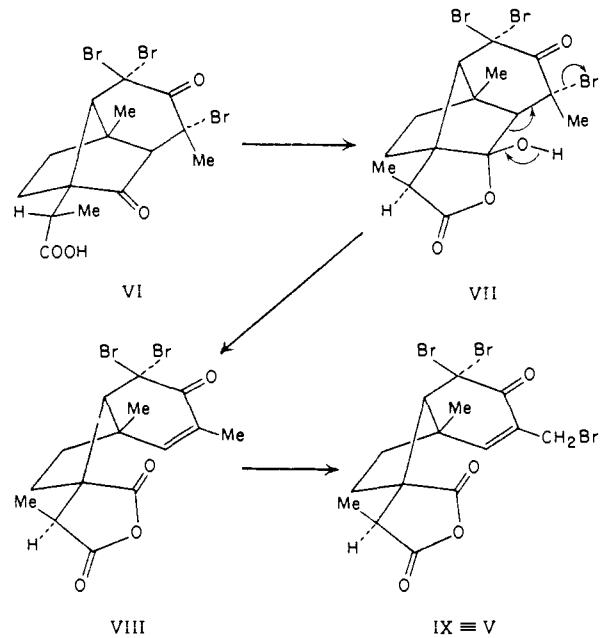


V

corresponding to two hydrogen atoms with $\tau = 5.61$ and 5.89 p.p.m. and $J = 10$ c.p.s. can be assigned to the bromomethyl group.[15] A singlet at $\tau = 6.49$ p.p.m. is attributable to the angular hydrogen atom, a multiplet centered at $\tau = 6.92$ p.p.m. to the hydrogen atom on the anhydride ring, and a complex series of peaks centered at $\tau = 7.92$ p.p.m. corresponding to *ca.* four hydrogen atoms to the hydrogen atoms of the methylene groups in the cyclopentane ring.[16] Thus tribromosantonin is assigned the structure V.

More detailed reference may now be made to the ultraviolet and infrared spectra of tribromosantonin. The high intensity ultraviolet maximum occurs at a wave length (246 m$\mu$) which is unusually high for a cyclohexenone with a single alkyl substituent on the double bond.[10] However, it has been observed in other cases that the substitution of bromine on the $\alpha'$-carbon atom of $\alpha,\beta$-unsaturated ketones can bring about bathochromic shifts of the same order as that observed here.[17] The end absorption observed in the ultraviolet spectrum of tribromosantonin is analogous to that reported previously for polybrominated compounds.[18,19] It may also be noted that the unusually high intensity of the long wave length maximum finds its counterpart in the hyperchromic effect of $\alpha$-substitution by bromine on the n $\rightarrow$ $\pi^*$ bands of saturated ketones.[19,20] The ketonic carbonyl-stretching band in the infrared spectrum of tribromosantonin (5.86 $\mu$) occurs at a considerably lower wave length than that of simple cyclohexenones (*cf.* IIIb, 5.98 $\mu$). The bulk of this shift may readily be attributed to the presence of an equatorial bromine atom on the $\alpha'$-carbon atom[17,21]; the bromomethyl group on the $\alpha$-carbon may also contribute to the shift.

The formation of tribromosantonin may be regarded as occurring by the following or a similar route



VI VII VIII IX ≡ V

In this scheme, bromination of santonic acid (I) gives the tribromo compound VI which may exist in equilibrium with the tautomer VII, favored by the high degree of substitution of the lactol ring.[22] The change VII $\rightarrow$ VIII is closely analogous to the "1,4-elimination with fragmentation" reactions codified and investigated by Grob[23]; the anticipated stereochemistry of the intermediate VII would favor such a reaction. Several routes may be envisaged for the conversion of VIII to V, but there is at present no evidence which provides a basis for choice.

## Experimental[24]

**Tribromosantonin** (V). (i).—Santonic acid (4.9 g., 0.0186 mole) was dissolved in chloroform (25 ml.) and 2 drops of water were added to the solution. The mixture was cooled and swirled in an ice-bath and to it was added a solution of bromine (6 ml., 0.117 mole) in chloroform (6 ml.) over a period of 30 minutes. No reaction was evident during the first 8 minutes of addition, but thereafter a slight effervescence was observed, the red color rapidly changed to a pale yellow-green, and the temperature of the mixture rose by 5–10°. Subsequent bromine addition caused a gradual reappearance of the red color. After the addition was complete, the mixture was allowed to stand in the ice-bath for a period of 3 hours, throughout which time hydrogen bromide was evolved. The chloroform solution was then washed three times with saturated sulfurous acid and three times with saturated aqueous sodium carbonate. The organic layer was dried by being shaken with concentrated aqueous sodium chloride and allowed to stand over anhydrous magnesium sulfate. Removal of solvent at room temperature *in vacuo* left 6.5 g. of yellow semi-solid product. Trituration of the residue with warm ethanol followed by crystallization of the resulting solid from ethyl acetate–cyclohexane gave tribromosantonin (1.1 g., 12%) as colorless needles, m.p. 195–198° dec. (cap. tube inserted at 180°); infrared bands ($CHCl_3$): 5.45, 5.66, 5.86, 6.12(w) $\mu$.

*Anal.* Calcd. for $C_{15}H_{15}O_4Br_3$: C, 36.10; H, 3.03; Br, 48.05. Found: C, 36.22, 36.34; H, 3.22, 3.20; Br, 48.83, 48.72.

(ii).—A solution of santonic acid (2.5 g., 0.0095 mole) in acetic acid (25 ml.) was cooled in a bath at 15° and bromine (0.5 ml.) was added. Reaction began after 2 minutes resulting in decolorization; further bromine (3 ml., 0.069 mole total) was then added. After standing for 3 hours at 15° the reaction mix-

(14) *Cf.* ref. 13, p. 87.

(15) P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957), have found $J = 10 \sim 11$ c.p.s. for coupling between the protons of the $CH_2Br$ group in methyl 2,3-dibromo-2-methylpropanoate; *cf.* also, J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

(16) The $\tau$-values of these peaks and of those discussed earlier reflect the additive secondary effects of the unusually large number of electron-withdrawing groups in the tribromosantonin molecule.

(17) M. Fieser, A. Romero and L. F. Fieser, *J. Am. Chem. Soc.*, **77**, 3305 (1955); A. Romero, Ph.D. Thesis, Harvard University, 1954.

(18) M. Pestemer and H. Duftschmid, *Monatsh.*, **73**, 254 (1940).

(19) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(20) R. C. Cookson, *ibid.*, 282 (1954).

(21) *Cf.* R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

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

(23) C. A. Grob, "Theoret. Org. Chem., Papers Kekulé Symposium, London," 1958, p. 114 (1959); C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

(24) Melting points are uncorrected.

ture was distilled at the pressure of the water aspirator with occasional warming on the steam-bath. Acetic acid and unreacted bromine were thus removed and a pale yellow crystalline solid remained. This product was digested with boiling ether for a few minutes and filtered to give almost colorless crystals (1.96 g., 41%), m.p. 180–185° dec. Recrystallization from ethyl acetate–cyclohexane afforded colorless needles, m.p. 195–200° dec. (cap. tube inserted at 180°), undepressed on admixture with the product obtained by bromination in chloroform; the infrared spectra of the two products were identical; ultraviolet maxima ($CH_3CN$)[25]: 246 mμ (log ε 3.72), 323 mμ (log ε 2.26).

*Anal.* Calcd. for $C_{15}H_{15}O_4Br_3$: C, 36.10; H, 3.03; Br, 48.05. Found: C, 35.96; H, 2.99; Br, 48.12.

**Hydrolysis of Tribromosantonin.**—Tribromosantonin (0.2 g.) and an aqueous solution (25 ml.) of sodium bicarbonate (1.1 g.) were boiled under reflux. The tribromosantonin dissolved slowly and after about 15 minutes a brown amorphous solid began to separate from the solution. After 30 minutes the reaction mixture was cooled and filtered. The clear, red-brown filtrate was washed with ether and acidified. The turbid liquid was extracted with ether and the extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of solvent at room temperature *in vacuo* left an acidic brown gum (*ca.* 0.050 g.) from which no crystalline product could be obtained.

**Reduction of Tribromosantonin with Chromous Chloride. Formation of II and IIIb.**—A three-necked round-bottomed flask was fitted with a gas inlet tube, a wide rubber sleeve connected to an erlenmeyer flask, and an outlet tube fitted with a sintered glass filter end leading *via* a stopcock to the reaction vessel; the outlet tube was initially raised above the contents of the flask. A solution of chromic chloride (20 g.) in 95% ethanol (140 ml.) and concentrated hydrochloric acid (30 ml.) was placed in the round-bottomed flask and granulated zinc (16 g.) was placed in the erlenmeyer flask. The apparatus was thoroughly purged of air with nitrogen and the zinc was added to the solution in portions over a period of 10 minutes. After 4 hours the reduction of chromic chloride to chromous chloride was complete as evidenced by the change in the color of the solution from deep green to pale blue. The outlet tube was then lowered into the solution so that the sintered glass filter end dipped well beneath the surface. Chromous chloride solution (0.75 *M*) was then forced out by means of nitrogen pressure into the reaction vessel.

Tribromosantonin (0.90 g., 0.0018 mole) dissolved in acetone (40 ml.) was treated with chromous chloride solution (12 ml.) prepared in this manner. After standing for 2 hours at room temperature, the reaction mixture was brought to *p*H 6 with sodium bicarbonate and most of the acetone and ethanol were removed by distillation at room temperature *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal solution was extracted with saturated aqueous sodium bicarbonate and the aqueous layer was acidified and extracted with ether. This ethereal extract was dried over anhydrous magnesium sulfate and was freed of solvent. The residue was a viscous oil (0.25 g.) which could not be induced to crystallize; the oil had infrared bands ($CHCl_3$) at 2.9–3.5, 5.79 and 6.00 μ, and an ultraviolet maximum (95% EtOH) at 238 mμ.

(25) The spectrum of tribromosantonin in ethanolic solution had similar maxima; measured values of extinction coefficient were unreliable in this case, however, because of rapid decomposition, as witnessed by a brown coloration of the solution.

The oily reduction product (0.10 g.) was heated in a sublimation apparatus at 140° and 0.3 mm. pressure; a colorless oil distilled which solidified completely on scratching. The white solid (0.015 g., 8% based on tribromosantonin) had m.p. 160–165° and gave a negative test for halogen. Recrystallization of the product from ethyl acetate–cyclohexane afforded white needles, m.p. 168–172°; infrared bands ($CHCl_3$): 5.45, 5.65, 5.98 μ; ultraviolet maxima (95% EtOH): 237 mμ (log ε 4.00), 323 mμ (log ε 1.61).

*Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.20; H, 6.99.

**Reduction of Tribromosantonin with Zinc and Acetic Anhydride. Formation of IIIb.**—Acetic anhydride (200 ml.) was added to a solution of tribromosantonin (15 g., 0.030 mole) in ethyl acetate (400 ml.). The solution was boiled under reflux with mechanical stirring and to it was added zinc dust (75 g.) over a period of 1 hour. The hot mixture was filtered and the filtrate was concentrated to small volume *in vacuo;* the concentrate was taken up in ether (100 ml.). The ethereal solution was washed with water containing a few ml. of dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and freed of solvent. The crude product (3.1 g., 40%) remained as a yellow crystalline solid, m.p. 155–165°. Two recrystallizations from ethyl acetate–cyclohexane afforded white needles (1.2 g.), m.p. 168–172°, undepressed on admixture with the product, m.p. 168–172°, obtained *via* chromous chloride reduction; the infrared spectra of the two products were identical.

*Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.66; H, 6.93.

Hydrolysis of this product with warm aqueous sodium bicarbonate gave an acid, m.p. 162.5–164.5°, whose infrared spectrum was very similar to that of the acidic gum obtained by reduction of tribromosantonin with chromous chloride.

Hydrogenation of the zinc reduction product in ethyl acetate solution over 10% palladium–charcoal proceeded with the uptake of one molar equivalent of hydrogen and the formation of a white crystalline product, m.p. 110–112°; infrared spectrum ($CHCl_3$): 5.45, 5.64, 5.83 μ; no high intensity ultraviolet absorption.

**Ozonolysis of IIIb. Formation of α-Santoric Acid (IV).**—A solution of IIIb (0.40 g., 0.0015 mole) in ethyl acetate (20 ml.), cooled in an acetone–Dry Ice mixture, was treated with a stream of ozonized oxygen until the effluent gas gave a positive test for ozone in a potassium iodide trap. Solvent was then removed from the reaction mixture below −5° at 0.01 mm. pressure. The residual oil was treated with boiling water (5 ml.) containing 30% hydrogen peroxide (0.5 ml.) for 10 minutes. Platinum oxide (0.01 g.) was added to the cooled aqueous solution to decompose any remaining hydrogen peroxide and the solution was subjected to continuous extraction with ether overnight. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated at room temperature yielding a pale yellow, viscous oil (0.200 g.). This residue was dissolved in acetonitrile (1 ml.) and the solution was kept at 5° for 3 days. The solid which separated was filtered and recrystallized once from acetonitrile and twice from ether–chloroform, affording white crystals (0.020 g.), m.p. 182–183°. A mixture of this product with α-santoric acid,[11] m.p. 184–185°, had m.p. 183–184.5°. The infrared spectra (Nujol) of the product and of α-santoric acid were identical.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.]

# Oxidative Cleavage of Tyrosyl–Peptide Bonds. III. Synthesis and Cleavage of Peptides Containing Sulfur Moieties[1]

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RECEIVED SEPTEMBER 21, 1962

A series of N-acylated tyrosyl-S-alkylcysteine dipeptides was found to undergo facile oxidative cleavage with N-bromosuccinimide. Similar cleavage occurs, without difficulty, in simple tyrosylcystine peptides. Evidence is presented for intramolecularly-catalyzed ester hydrolysis in β-sulfoalanine *t*-butyl ester. The preparation of cystine di-*t*-butyl ester is described.

The oxidative splitting of tyrosyl–peptide bonds (I → II) by the use of N-bromosuccinimide (NBS) has been applied to a variety of tyrosine derivatives and simple peptides.[1] Despite the apparent generality of the reaction, evidence was at hand to indicate that some difficulty might be encountered in the cleavage of tyrosyl–cysteine bonds. Thus, it had been observed by du Vigneaud and his associates that tyrosylcysteic acid failed to undergo oxidative cleavage with bromine

(1) For paper II, *cf.* G. L. Schmir and L. A. Cohen, *J. Am. Chem. Soc.*, **83**, 723 (1961).

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