

ORGANIC AND BIOLOGICAL CHEMISTRY

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

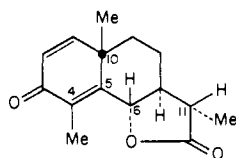
The Structure of γ -Metasantonin¹

BY R. B. WOODWARD AND PETER YATES

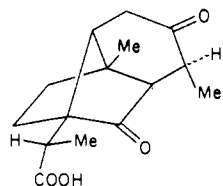
RECEIVED JULY 30, 1962

γ -Metasantonin, the product of the action of concentrated sulfuric acid on santonic acid or metasantonin acid, is shown to have the structure VIII.

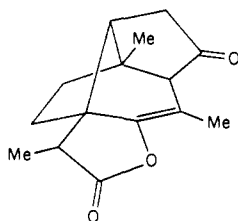
Santonin acid, $C_{15}H_{20}O_4$, the product of the action of strong alkalis on santonin (I), possesses the structure II.²⁻⁴ The establishment of this constitution precipitated an unusual situation, in that steric factors bar



I



II



III

the loss of the elements of water from the molecule of II in any simple way,⁶ and, yet, *no less than five isomeric dehydration products*, $C_{15}H_{18}O_3$, had been derived from santonic acid under the influence of divers reagents. Two of these substances, santonide and parasantonide, have been shown to be stereoisomerides of the structure III through earlier studies in this Laboratory.⁶ In this and the following communication⁷ the structures of the remaining three— α -, β - and γ -metasantonin—are elucidated.

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

(2) (a) R. B. Woodward, F. J. Brutschy and H. Baer, *J. Am. Chem. Soc.*, **70**, 4216 (1948). (b) R. B. Woodward and P. Yates, *Chem. Ind. (London)*, 1391 (1954). The numbering system adopted in the present communication conforms to that now in general usage and differs from that used by us earlier.

(3) The absolute configuration follows from its relationship to santonin, whose absolute configuration is known: M. Sumi, *Pharm. Bull.*, **4**, 158 (1956); H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 858 (1956); C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

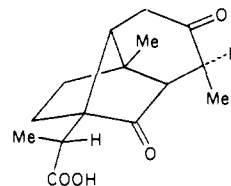
(4) The question^{2b,5} of the configurational assignment at C.11 in santonin is relevant to the assignment at C.11 in santonic acid since these configurations are directly interrelated. The matter appears to have been resolved recently with the establishment of the α -orientation of the C.11 methyl group [J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 111 (1962); D. H. R. Barton, T. Miki, J. T. Pinkey and R. J. Wells, *ibid.*, 112 (1962); M. Nakazaki and H. Arakawa, *ibid.*, 151 (1962)], contrary to the view set forth in our earlier publication.^{2b} In this and the following papers, we have adopted the new assignment for santonin, santonic acid and, where applicable, their transformation products.

(5) H. Mitsuhashi, *J. Pharm. Soc. Japan*, **71**, 1115 (1951); E. J. Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955); T. Miki, *J. Pharm. Soc. Japan*, **75**, 416 (1955); W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955); Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. Ind. (London)*, 953 (1956); W. Cocker and T. B. H. McMurry, *ibid.*, 1430 (1956); M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 1268 (1958); cf. also, W. G. Dauben, W. K. Hayes, J. S. P. Schwarz and J. F. McFarland, *J. Am. Chem. Soc.*, **82**, 2232 (1960).

(6) R. B. Woodward and E. G. Kovach, *ibid.*, **73**, 1009 (1950).

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

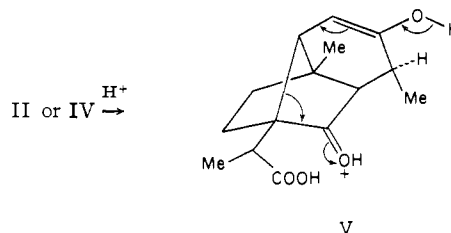
We consider here γ -metasantonin.⁸ This compound is the product of the action of warm concentrated sulfuric acid on santonic acid, or the stereoisomeric metasantonin acid (IV).⁹



IV

Three facets of the chemistry of γ -metasantonin command special attention and provide the key to its structure: (i) it is reconverted to metasantonin acid on dissolution in base⁹; (ii) it is readily reduced, by zinc and hydrochloric acid^{9b,10} or acetic acid,¹⁰ or catalytically,¹¹ to a dihydro derivative, $C_{15}H_{20}O_3$; (iii) both γ -metasantonin and dihydro- γ -metasantonin form oximes.^{9b,10} The first of these observations tends to confirm the simple view that γ -metasantonin is a lactone and demonstrates that its formation, unlike that, for example, of parasantonide (III), is not accompanied by rearrangement of the carbon skeleton of santonic acid. The second clearly suggests the presence, in the molecule of the lactone, of a carbon-carbon double bond conjugated with a carbonyl group, the presence of which is shown by formation of an oxime.

It seemed to us not unlikely that the latter system might have its origin in the susceptibility of santonic acid to the cleavage reaction symbolized in V (arrows); it is worthy of note that such a change would represent,



V

in effect, the reversal of a key step, *viz.*, the formation of the carbon-carbon bond by an internal Michael reaction, in the formation of santonic acid from santonin.² The proximate product, VI, of the cleavage here suggested, is freed from steric barriers to lactonization,¹² and we may write the expression VII as a possible one for γ -metasantonin. Generalized ex-

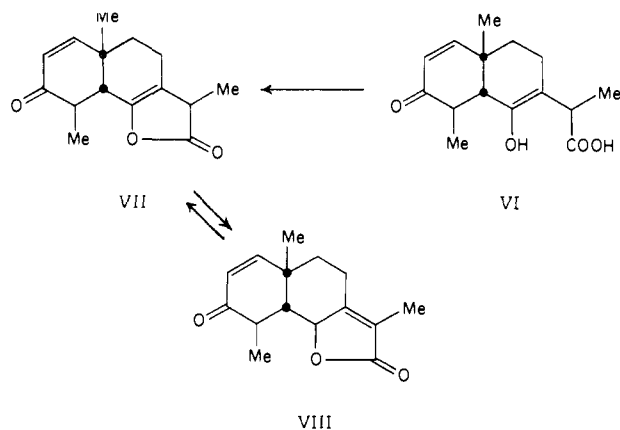
(8) This compound has hitherto been called simply metasantonin (*cf.* ref. 9b). This terminology has resulted in some confusion, in view of the existence of the α - and β -metasantonins (*cf.* ref. 7) of which the latter possesses a common melting point with "metasantonin." We suggest that the adoption of the name γ -metasantonin will dispel further confusion.

(9) (a) S. Cannizzaro and L. Valente, *Atti reale accad. Lincei, Transunti*, **III**, **8**, 242 (1879); (b) L. Francesconi, *Gazz. chim. ital.*, **25**ii, 461 (1895).

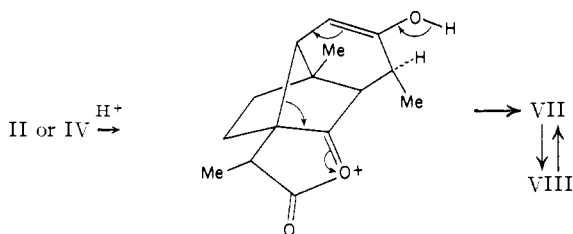
(10) L. Francesconi, *ibid.*, **29**ii, 181 (1899).

(11) W. F. von Oettingen, Dissertation, Göttingen, 1913.

(12) Indeed, the formation of the lactone ring may well be concomitant with the reverse Michael reaction.

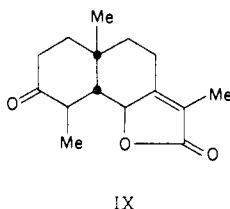


perience suggests¹³ that the tautomeric molecule VIII would be more stable than VII and since the conditions of formation of γ -metasantonin may be presumed to be capable of mobilizing the equilibrium



VII \rightleftharpoons VIII, we considered VIII as perhaps the most likely structure for the lactone.^{14,15} The new evidence now to be described demonstrates the correctness of this view.

Clear confirmatory evidence of the presence in γ -metasantonin of the functions in VIII was obtained through physical measurements. The infrared spectrum of the lactone contains bands at 5.72 and 5.94 μ . The first of these is attributable to the α,β -unsaturated five-membered lactone carbonyl group, while the second is characteristic of a normal carbonyl group, conjugated with a lightly substituted double bond. The expression VIII for γ -metasantonin implies IX for dihydro- γ -metasantonin, and this view receives support from the



appearance in the infrared spectrum of the latter of bands at 5.71 μ (unchanged α,β -unsaturated lactone system) and 5.84 μ (normal, unconjugated carbonyl group). The ultraviolet absorption spectrum of γ -metasantonin, λ_{\max} 220 $m\mu$ ($\log \epsilon$ 4.31), 327 $m\mu$ ($\log \epsilon$ 1.48), is that which would be expected from the addition of bands characteristic of isolated β -monosubstituted α,β -unsaturated carbonyl and α,β,β -trisubstituted α,β -unsaturated γ -lactone systems¹⁶; in particular, the high intensity of the low wave length band may be noted.

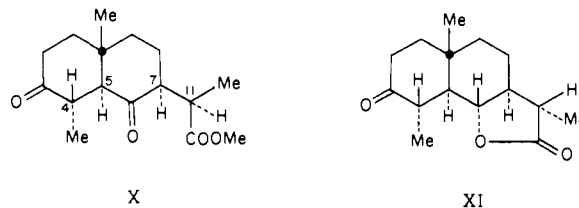
(13) Cf. (a) W. Cocker and S. Hornsby, *J. Chem. Soc.*, 1157 (1947); (b) L. J. Haynes and E. R. H. Jones, *ibid.*, 954 (1956).

(14) It may be noted that the formation of γ -metasantonin from both santoninic acid and metasantoninic acid supports this formulation in that these acids differ only in their configuration at C.11 (*cf. ref. 2b and 4*), and the asymmetry of this center is destroyed in the structure VIII.

(15) The *cis* ring fusion shown in VIII is considered to be that most likely to obtain; however, the possibility of the epimerization of VI or VII in the strongly acid medium to the corresponding *trans* fused compounds, resulting in a final product with *trans* ring fusion, cannot be excluded.

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

Conclusive proof of the close relationship between santonin and γ -metasantonin implied by the structure VIII for the latter was obtained by conversion of both lactones into the diketo ester X by simple hydrolytic, reductive and oxidative processes. Thus, dihydro- γ -metasantonin was converted by hot aqueous sodium hydroxide into a sirupy diketo acid¹⁷ and thence, with diazomethane, to the diketo ester X, m.p. 185.5–187.5°. On the other hand, the identical ester was prepared from α -tetrahydrosantonin (XI)^{4,18} through



hydrolysis of the lactone function by base and esterification of the resulting hydroxy acid with diazomethane, followed by chromic acid oxidation, vigorous basic hydrolysis and re-esterification. It is worthy of note that the same fortunate circumstances which deprived these experiments of stereochemical complications suggest the assignment of configurations to the diketo ester as in X. Thus with the exception of C.10, all of the ring asymmetric centers (C.4, C.5 and C.7) are adjacent to carbonyl groups, and consequently susceptible to inversion under basic conditions; in these circumstances, the most stable isomer will be produced and it is most likely that this will be that isomer, X, all of whose equilibratable bonds are equatorial.¹⁹

The formation of metasantoninic acid from γ -metasantonin with base deserves some comment. The behavior of γ -metasantonin with base may be expected to parallel that of the dihydrolactone (*vide supra*) and lead initially to the unsaturated diketo acid XIII.¹⁷ This is the same intermediate which is involved in the conversion of β -santonin (XII) into metasantoninic acid (XIV \equiv IV).^{2,4}

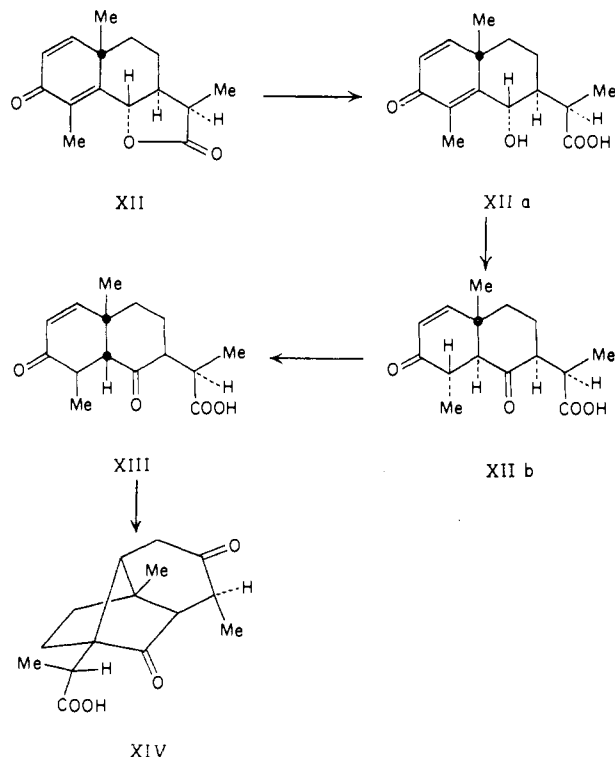
Experimental

γ -Metasantonin (VIII).—Santoninic acid (9.0 g.) was heated with concentrated sulfuric acid (50 ml.) on the steam-bath for 3 hours. The black solution was cooled to room temperature and poured slowly with stirring onto crushed ice (1.5 kg.). The mixture was made slightly basic by the addition of solid sodium carbonate and was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and the ether was distilled until crystallization began. The deposit (3.6 g.) of brown crystalline material was filtered and recrystallized from a large

(17) The conversion of the α,β -unsaturated γ -lactone to a γ -keto acid system presumably occurs *via* the β,γ -unsaturated isomer (*cf. ref. 13a*).

(18) H. Wienhaus and W. F. von Oettingen, *Ann.*, **397**, 219 (1913); W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956); M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957), and references therein quoted.

(19) The configuration at C.11 is assumed to be congruent with that at the similar position in metasantoninic acid,^{2b,4} since the latter acid is formed when γ -metasantonin itself is treated with base. Since the completion of our work, J. C. Banerji, D. H. R. Barton and R. C. Cookson (*J. Chem. Soc.*, 5041 (1957)) have published an account of the preparation of five stereoisomeric esters of type X, one of which—the dimethyl ν -3,6-dioxo-eudesmanoate of m.p. 187–188°—is very probably identical with our ester. The configuration tentatively assigned to the ν -ester by Barton, *et al.*, differs from that put forward here. We retain our preference for the structure X, while recognizing that a rigorous solution of the stereochemical problem is not possible without further experimentation. Further, H. Matsumuna, I. Iwai and E. Ohki (*J. Pharm. Soc. Japan*, **74**, 1206 (1954); **75**, 1043 (1955)) have converted α -tetrahydrosantonin (XI) by hydrolysis, oxidation and esterification to a diketo ester of m.p. 79–81° which is considered by Barton, *et al.*, to be identical with their dimethyl α -3,6-dioxo-eudesmanoate. The sequence of reactions by which this product was obtained from XI, unlike that used in our work for the preparation of X from XI, did not permit equilibration at the C.11 position in the diketo ester. We therefore provisionally consider this product to be the epimer of X at C.11, in conformity with the views of Barton, *et al.* It should be mentioned that these matters of stereochemical detail are not relevant to our main demonstration.



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 $m\mu$ ($\log \epsilon$ 4.31) and 327 $m\mu$ ($\log \epsilon$ 1.48); molecular weight (isothermal distillation, CHCl_3 , 25°) 254; calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_3$, 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 $m\mu$ ($\log \epsilon$ 4.19) and 287 $m\mu$ ($\log \epsilon$ 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 $m\mu$ ($\log \epsilon$ 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 ($15 \times 1.5 \text{ cm.}$); 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 - β_3 , β_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

RECEIVED JULY 30, 1962

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.

