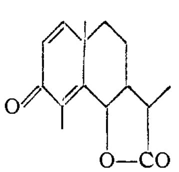
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

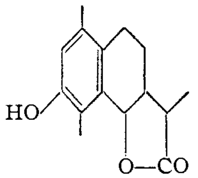
# The Structure of Santonic Acid

BY R. B. WOODWARD, F. J. BRUTSCHY* AND HAROLD BAER

The long series of investigations[1] which culminated in the proposal of the structure (I) for santonin in 1930 by Clemo, Haworth and Walton[2] developed along three lines; *viz.*, direct oxidative degradation, on the one hand, and on the other, extensive studies of two transformation products of santonin, *desmotropo*santonin (II) and santonic acid. While the new formulation permitted a decisive clarification of the results obtained in the first two lines of attack, and while there would no longer seem to be any question of the validity of the expression (I), none the less, the situation has been unsatisfactory in so far as all attempts at the rational formulation of santonic acid and the extensive series of substances derived from it by degradation have failed.[3]



I



II

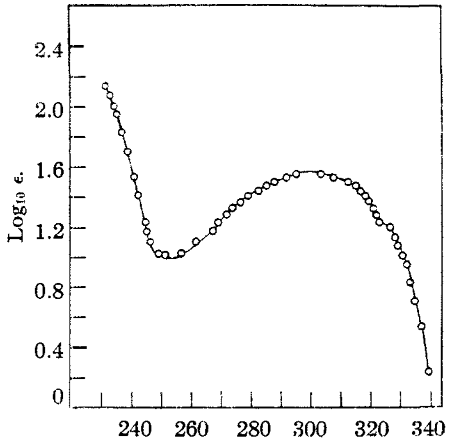
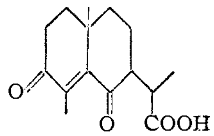


Fig. 1.

Santonic acid, $C_{15}H_{20}O_4$, is readily formed from santonin by the action of hot concentrated aqueous bases,[4] preferably potassium hydroxide.[5] It is a monobasic acid and possesses two carbonyl groups.[6] Bromine does not add to it, and permanganate oxidizes it only slowly. The molecule would, therefore, appear to be saturated and consequently tricyclic. Further evidence in this direction is afforded by the fact that reduction by various chemical agents leads to a dihydrosantonic acid which differs from the parent substance in having a secondary alcohol group in place of one of the original carbonyl groups.[7] If the likely assumption is made that these carbonyl groups are situated at the points of attachment of the carbonyl and (potential) hydroxyl groups of the original santonin molecule it is evidence that a double bond, if present, could be only in the highly improbable $\Delta^5$- or $\Delta^6$-position; otherwise, it would be conjugated with one or both of the carbonyl groups and would not survive under reducing conditions. We have confirmed these conclusions by an examination of the ultraviolet absorption spectrum of santonic acid (Fig. 1).[8] The position ($\lambda_{max.} = 301$ mμ) and intensity ($\epsilon_{max.} = 1.56$) of the absorption band are characteristic of the simple unconjugated carbonyl system and the absence of a high intensity band in the short wave length region[9] definitely excludes the possibility of a double bond in conjugation with either of the carbonyl groups. In the light of these observations the formula (III) proposed for santonic acid by Abkin and Medvedev[10] cannot be considered seriously.



III

The Italian school, and in particular Francesconi, has made a careful and fruitful study of the degradation of santonic acid. By oxidation with

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(1) The Italian school, led by Cannizzaro, pursued work in this field indefatigably and with brilliant experimental results for more than fifty years (for reviews of the work at various stages, *cf.* Cannizzaro, *Ber.*, **18**, 2746 (1885); Grassi-Cristaldi and Gucci, *Gazz. chim. ital.*, **22i**, 1 (1892); Cannizzaro and Gucci, *ibid.*, **23i**, 286 (1893); Andreocci, *Ber.*, **26**, 1375 (1893), and *Gazz. chim. ital.*, **25**, 452 (1895); Francesconi, *ibid.*, **29ii**, 182 (1899); Angeli and Marino, *Rend. accad. Lincei*, **16i**, 159 (1907); Bargellini, *ibid.*, **16ii**, 264 (1907); Francesconi and Cusmano, *Gazz. chim. ital.*, **38ii**, 109 (1908); Angeli, *Rend. accad. Lincei*, **33**, 10 (1924). Wedekind and his students also carried out extensive studies (see Wedekind and Jäckh, Studies on Santonin, XIX, *J. prakt. Chem.*, **139**, 129 (1934) for references). *Cf.* also Ruzicka and Eichenberger, *Helv. Chim. Acta*, **13**, 1117 (1930), and refs. 2 and 20.

(2) *J. Chem. Soc.*, 1110 (1930); *cf.* also Clemo, Haworth and Walton, *ibid.*, 2368 (1929); Clemo and Haworth, *ibid.*, 2579 (1930).

(3) *Cf.* Wedekind and Engel, *J. prakt. Chem.*, **139**, 115 (1934), for the most recent statement of the problem.

(4) Hooslef, *Förhandlingar vid Skandinaviska Naturforskavemötat*, 304 (1863); Cannizzaro and Sestine, *Gazz. chim. ital.*, **3**, 241 (1873); Schiff and Florenz, *Ber.*, **6**, 1201 (1873).

(5) v. Oettingen, Dissertation, Göttingen, 1913; *cf.* also ref. 3.

(6) Francesconi, *Gazz. chim. ital.*, **29ii**, 181 (1899).

(7) Cannizzaro, *ibid.*, **6**, 341 (1876), and ref. 3.

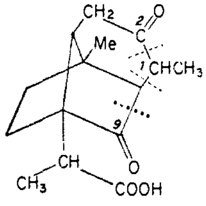
(8) We wish to thank Mr. J. J. Leavitt for his kindness in carrying out this determination.

(9) Woodward, THIS JOURNAL, **63**, 1123 (1941).

(10) Abkin and Medvedev, *J. Gen. Chem.* (*USSR*), **4**, 1407 (1934).

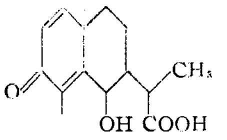
potassium permanganate, the latter is converted to santoric acid, $C_{13}H_{18}O_8$. The new acid is saturated and tetrabasic and, therefore, contains one ring. Santoric acid on fusion with potassium hydroxide gives one mole of acetic acid and santoronic acid, $C_{10}H_{16}O_6$, a saturated, tribasic, and consequently, acyclic acid. The latter, on further treatment with potassium hydroxide at a higher temperature, is converted to the saturated monocyclic ketone, santorone, $C_8H_{14}O$.[11]

These observations are readily and, taken with other facts, uniquely explicable in terms of the structure (IV) for santonic acid. The expression

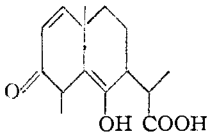


IV

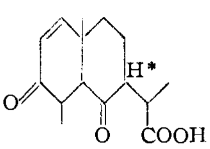
may be deduced from a rational consideration of the effects to be anticipated in the action of strong bases on the santonin molecule. Thus, the proximate product of the action of bases on santonin, santoninic acid (V), in its character as an α,β-unsaturated carbonyl compound, is equilibrated under the reaction conditions with the corresponding β,γ-unsaturated isomer (VI). Since the latter is an unstabilized enol, it is transformed substantially irreversibly to the ketone (VII). The net change (V → VII) finds a precise parallel in the conversion of 3-hydroxy-6-ketocholestene-4 to 3,6-diketocholestane.[12] Now the molecule of VII contains a hydrogen atom (starred), activated by an adjacent carbonyl group, and five carbon atoms removed from the β-carbon atom of an α,β-unsaturated carbonyl system. These circumstances are ideal for the occurrence of an internal Michael condensation, with the formation of a new five-membered ring, leading to VIII (≡ IV).[13] The new tricyclic system has only the small amount of strain characteristic of the [1,2,2]-*bicyclo* heptane system of camphor: this relation, which tends to be obscured in the planar formula (VIII), is readily evident on examination of the expression (IV).



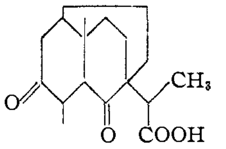
V



VI

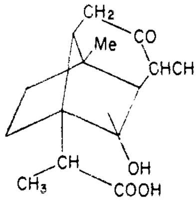


VII

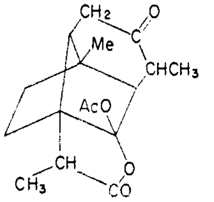


VIII

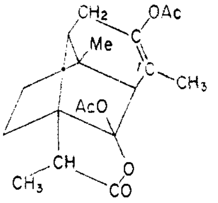
We turn now to the examination of the degree to which the properties to be expected of a molecule of the structure (IV) agree with those actually observed for santonic acid. In accord with the prerequisites outlined above, (IV) is a saturated, diketonic, monobasic acid, $C_{15}H_{20}O_4$. It is worthy of note that space models of (IV) demonstrate that the C.2 carbonyl group is considerably more hindered than that at C.9. Accordingly, the monophenylhydrazone[6] and monoxime[6] of santonic acid are very probably formed by condensation at the latter position, while dihydrosantonic acid[3,7] may be formulated adequately as IX. Satisfactory representations of the mono- and diacetyl derivatives[3,7] of santonic acid are achieved in (X) and (XI).



IX



X



XI

The most convincing evidence for the structure (IV) is obtained through a consideration of the degradation of santonic acid. On permanganate oxidation of IV, cleavage adjacent to the carbonyl groups (dotted lines) would be expected, with the formation of an acid (XII = XIIa).[14] (XII) is a saturated, monocyclic, tetrabasic acid, $C_{12}H_{18}O_8$, and in these, and all other respects, represents a completely adequate expression for santoric acid, the product of the action of permanganate on santonic acid. Santoric acid forms a monoanhydride[11] and two isomeric dianhydrides.[11] The formation

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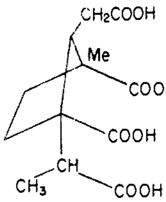
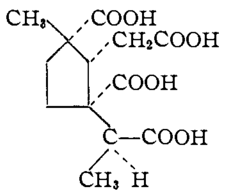
(11) Francesconi, *Gazz. chim. ital.*, **22*i***, 181 (1892); *ibid.*, **23*ii***, 457 (1893); *ibid.*, **29*ii***, 224 (1899); *Rend. accad. Lincei, V*, **5*ii***, 214 (1896).

(12) Heilbron, Jones and Spring, *J. Chem. Soc.*, **801** (1937); Butenandt and Schramm, *Ber.*, **69**, 2289 (1936); *cf.* also Woodward and Blout. THIS JOURNAL, **65**, 562 (1943).

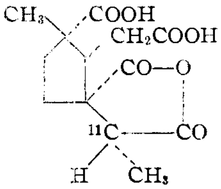
(13) In artemisin, the 8-position is occupied by a hydroxyl group, in dihydro- and tetrahydrosantonin and in 8-oxysantonin the $\Delta^3$-double bond is missing, in monochlorosantonin the 3-chloro substituent tends to diminish the polarity of the $\Delta^3$-double bond, and in artemionic acid, the $\Delta^{(10)1}$-double bond does not permit the construction of the tricyclic system of IV. In the light of our proposals, then, the failure (*cf.* ref. 3) of each of these substances to undergo a change analogous to that of santonin to santonic acid is not surprising.

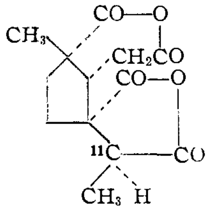
(14) The dotted lines in XIIa indicate that the attached groups are *below* the five-membered ring.

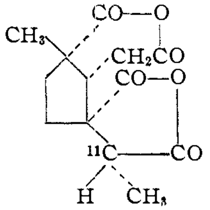

XII

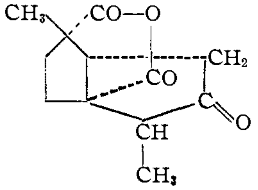

XIIa

of the monoanhydride by the action of heat on the acid is accompanied by inversion at an asymmetric center, since subsequent hydrolysis leads to a new isomeric β-santoric acid; from the latter, the same anhydride, which is very probably the substituted succinic anhydride (XIII), is formed. The presence of the –CO–O– group adjacent to C.11 permits the ready epimerization. The α-dianhydride (XIV), obtained by the action of acetic anhydride on α-santoric acid *in the cold*, is converted into a β-anhydride (XV) by heat; the latter, which differs from (XIV) only in the configuration at C.11, is also formed from either α- or β-santoric acid or from the monoanhydride (XIII) by the action of *hot* acetic anhydride, and gives on hydrolysis β-santoric acid. Further, the stable configuration of the anhydrides is the same as that of the acids, since β-santoric acid is formed from the α-acid by the action of mineral acids at elevated temperatures[11d]; the procedure is one which is well-known to effect epimerization of the asymmetric atom in the system $R'R\overset{*}{C}HCOOH$; the fact that only one isomeric acid is produced is at least presumptive evidence that, as required by XIIa, only one such invertible center is present in the molecule of santoric acid. Finally, (XII) permits the formulation as (XVI) of the keto-anhydride, $C_{12}H_{14}O_4$, obtained by drastic treatment of santoric acid with acetic anhydride.[11,15]

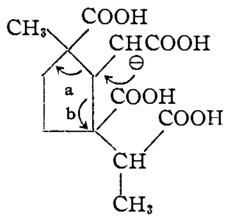

XIII


XIV

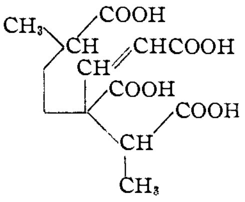

XV

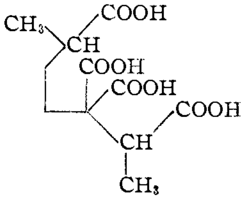

XVI

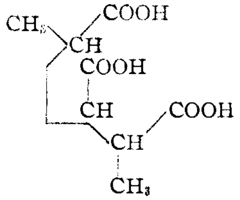
We consider next the further degradation of santoric acid by fusion with alkali to one molecule of acetic acid and santoronic acid. In our view, the following sequence of changes would be expected to attend the action of strong bases on XIIa: (1) loss of a proton from a carbon α- to a carboxyl group gives the anion XVII, which undergoes an inverse Michael reaction,[16] either in the sense a or b, giving an acyclic unsaturated acid (XVIII, from the change a; the final result of the shift in the alternate direction is the same, and need not be illustrated separately). (2) the unsaturated acid undergoes cleavage at the double bond to *acetic acid* and a new acid (XIX) containing two fewer carbon atoms (this change is analogous to the last step in the conversion of oleic acid to palmitic and acetic acids,[17] or undecylenic acid to *n*-nonylic and acetic acids[18] under the same conditions). (3) the malonic acid (XIX) loses carbon dioxide, giving the saturated, acyclic tribasic acid, $C_{10}H_{16}O_6$ (XX).[19] In this way, then, we deduce the expression (XX) for santoronic acid.



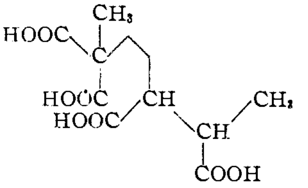
XVII

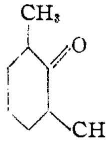

XVIII


XIX


XX

Further, *by direct comparison of the latter with a synthetic sample of 2,3,6-tricarboxyheptane, we have established that our structural conclusions are correct.* It is of interest that santoronic acid is a stereoisomer of the heptane tricarboxylic acid obtained by decarboxylation of the acid (XXI), which is itself formed directly by the permanganate oxidation of santonin[20] and which played so large a part in the final clarification of the structure of the lat-


XXI


XXII

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(15) Wedekind and Jäckh, *J. prakt. Chem.*, **139**, 131 (1934).

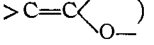
(16) Ingold and Powell, *J. Chem. Soc.*, **119**, 1976 (1921).

(17) Edmed, *ibid.*, **73**, 627 (1898).

(18) Chiozza, *Ann.*, **86**, 262 (1853).

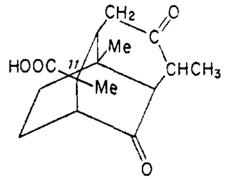
(19) So far as we are aware, considerations of this sort have not been applied hitherto to the prediction of the course of the alkali fusion of saturated cyclic acids; we believe that the scheme is generally applicable, and may be of value in other cases.

(20) Angeli and Morino, *Rend. accad. Lincei V*, **16**, 385 (1907).

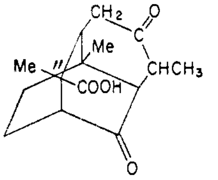
ter.[2,21] The optically active isomer, m. p. 88°, from (XXI), and the isomer, m. p. 134°, obtained by synthesis by Ruzicka,[21] whose method we used for the preparation of an authentic sample of (XX), are both converted by alkali fusion to a stable, racemic isomer, m. p. 127°. It is this latter form which is identical with santoronic acid, m. p. 127°, from natural sources; it will be recalled that the latter acid was isolated from an alkali fusion. In that connection, it may be pointed out that (XX) contains three asymmetric atoms, and consequently is capable of existence in four racemic and eight optically active forms. Each of the asymmetric atoms, however, is adjacent to a carboxyl group and it is clear that the action of alkali under extreme conditions brings about inversions (through the reaction $>\mathrm{CHCOO^-} \longrightarrow$  $>\mathrm{C{=}C}\left\langle {}^{\mathrm{O-}}_{\mathrm{O-}} \right.$ ) at such centers as are necessary to transform any particular isomer into the most stable form.

It is now clear that the final product of the degradation of santonic acid, santorone, obtained by the fusion of santoronic acid with alkali at very high temperatures, is 1,3-dimethylcyclohexanone-2 (XXII). This view is substantiated by the identical physical properties of the two ketones and by the fact that each forms an oxime melting at 117°.

Thus, the expression (IV) is a most satisfactory vehicle for the rationalization of the hitherto baffling chemistry of santonic acid. Some consideration must now be given to two alternative structures, (XXIII) and (XXIV).

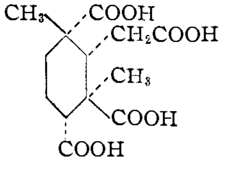


XXIII

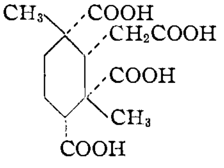


XXIV

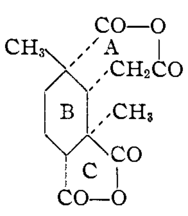
These structures, which differ only in the configuration at C.11, would be obtained if in the last step (the internal Michael reaction) of the scheme proposed for the formation of (IV), the removal of the hydrogen atom alpha to the *carboxyl*, rather than that alpha to the carbonyl group, were involved. Since the removal of a proton by base from the system $>\mathrm{CHCOO^-}$ is very much more difficult than from the system $>\mathrm{CHCOR}$, we consider this a much less likely alternative. Furthermore, the structures which follow for santoric acid (XXV *or* XXVI) on the basis of (XXIII *or* XXIV), while acceptable in so far as the further degradation to santoronic acid is concerned, are unsatisfactory in other respects. Thus, if santonic acid is (XXIII), then α-santoric acid is (XXV), the corresponding labile α-dianhydride (XXVII) has the *trans*-locking of rings B and C, and the stable β-dianhydride (XXVIII) is *cis*-fused.



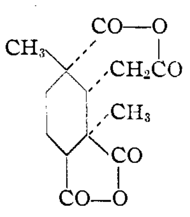
XXV



XXVI

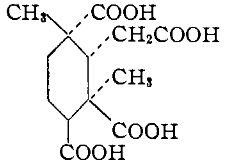


XXVII

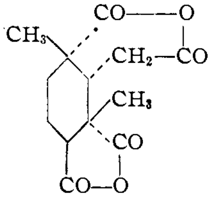


XXVIII

These relationships are in accord with generalized experience in fused bicyclic systems.[22] On the other hand, β-santoric acid in this scheme must have the *cis*-configuration (XXIX); experience in model cases suggests most strongly that the structure (XXV), having the *trans* arrangement of carboxyl groups, would be the stable isomer.[22] In the event that santonic acid had the alternative structure (XXIV), a similar contradiction of expected relative stabilities obtains, in this case in that the *trans* locked anhydride (XXX) must be assumed to be more stable than the *cis* isomer (XXXI). Further, if (XXV) or (XXVI) represent santoric acid, only the expression (XXXII) is possible for the keto-anhydride $C_{12}H_{14}O_4$. It may be doubted that the formation of bicyclic ketones from 1,4-dicarboxycyclohexanes will proceed nor-



XXIX



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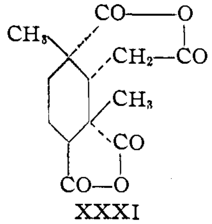
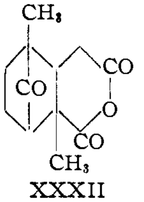


XXXI



XXXII

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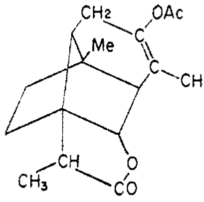
[21] Ruzicka and Steiner, *Helv. Chim. Acta*, **17**, 614 (1934).

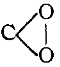
[22] In the case of the isomeric cyclohexane-1,2-dicarboxylic acids, the *trans*-acid and the *cis*-anhydride are the stable isomers (Hückel and Goth, *Ber.*, **58**, 447 (1925)). E. G. Davis (Dissertation, Harvard University (1942)) has shown that the same circumstances obtain in the rather more apposite case of the 1-methylcyclohexane-1,2-dicarboxylic acids. It must be pointed out that the presence of other groups in the 3- and 4- positions with respect to the invertible carboxyl group in (XXV–XXXI) might bring about a reversal in the rule that the *trans*-acid is the stable isomer of the pair, but is most unlikely to change the normal circumstance that *cis* locking of the fused six- and five-membered ring system is the stable arrangement.

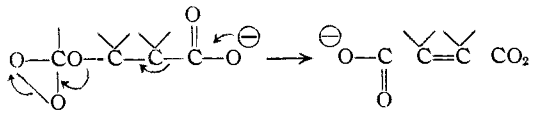
mally.[23] Finally, the formation from dihydrosantonic acid of an acetyl lactone,[3] readily formulable as (XXXIII) if (IV) be santonic acid, is clearly impossible on the basis of the structure (XXIII),



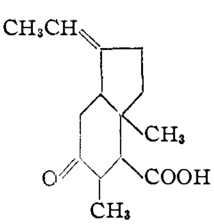
XXXIII

since the carboxyl group is on the other side of a ring as compared with either available position for a hydroxyl group.[24] We conclude that the expressions (XXIII) and (XXIV) are not acceptable for santonic acid.

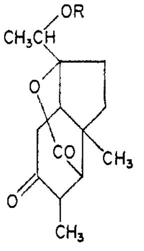
We turn now to the discussion of certain other interesting transformations of santonic acid. When treated with alkaline hydrogen peroxide, the latter undergoes a remarkable change to *apo*-santonic acid,[15] $C_{14}H_{20}O_3$, a keto acid containing one double bond. We suggest that the hydrogen peroxide attacks the more readily accessible C.9 carbonyl group of (IV), giving a peroxide,  (or a dimeric equivalent), and that the change



ensues; the resulting expression (XXXIV) for



XXXIV



XXXV

*apo*santonic acid contains the known features of the molecule, and, further, places the double bond and the carboxyl group in the special relationship demanded by our observation that perbenzoic acid attacks the molecule with the formation of a hydroxy-lactone, $C_{14}H_{20}O_4$, m. p. 193°, from which a mono-acetyl derivative, m. p. 160°, was obtained. These compounds may be formulated as (XXXV, R = H *or* Ac, respectively).

The isomeric substances santonide and parasantonide, $C_{15}H_{18}O_3$, deserve special comment, particularly in view of their extremely high optical rotatory power. The following chart summarizes the relationships between these substances and their congeners[25]

$$\begin{tikzcd}
\text{santonic acid } [\alpha]_D\ -74^\circ \arrow[r, "260^\circ"] \arrow[d, "\text{HOAc}"', "180^\circ"] \arrow[dr, "260^\circ", "\text{HOAc}"'] & \text{metasantonic acid } [\alpha]_D\ -90^\circ \arrow[d, "\text{HOAc}"', "260^\circ"] \\
\text{santonide } [\alpha]_D\ +744^\circ \arrow[d, shift left, "\text{OH}^-"] & \text{parasantonide } [\alpha]_D\ +897^\circ \arrow[d, shift left, "\text{OH}^-"] \\
\text{isosantonic acid } [\alpha]_D\ -74^\circ \arrow[u, shift left, "\text{Ac}_2\text{O}"] & \text{parasantonic acid } [\alpha]_D\ -98^\circ \arrow[u, shift left, "\text{Ac}_2\text{O}"]
\end{tikzcd}$$

Metasantonic acid, like santonic acid, gives $\alpha$-santoric acid (XII) on permanganate oxidation[11c]; thus, it is clear that metasantonic acid is simply epimeric with santonic acid (IV) at C.1.[26] It seems likely that this difference persists in, and is solely responsible for, the isomerism in the subsequent members of the series. It has been assumed generally in the past that the santonides were lactones, but no simple enol-lactone can be formed from IV, since the compact tetracyclic system of any such substance would have a double bond in an impossibly strained position. One of two assumptions must therefore be made: (i) the loss of water does not lead to a lactone *or*, (ii) the reaction is attended by rearrangement of the skeleton of the molecule. We are now engaged in a study of the structure of the santonides and at present favor the alternative (ii), but the final solution of the problem must await the accumulation of further experimental evidence.

## Experimental

**Santonic Acid.**—Since the details of von Oettingen's method,[5] which we have used for the preparation of santonic acid, are not readily available, we reproduce them here. Santonin (5.0 g.) was added to a solution of 11.2 g. of potassium hydroxide in 25 cc. of water. The reaction mixture was warmed on the steam-bath for half an hour, to dissolve the santonin, and then boiled vigorously for an hour. The solution was then cooled, acidified with 66 cc. of 12 *N* hydrochloric acid, and extracted with ether. When most of the ether had been evaporated, 2.5 g. of crystalline santonic acid separated, m. p. 165–168° (50%). Further small amounts of the acid could be obtained from the ether mother liquor by extraction with bicarbonate, etc. (to separate from recovered santonin).

**Santoric Acid** (*cf.* ref. 11a).—Santonic acid (1 g.) was dissolved in 50 cc. of water containing 4.0 g. of sodium car-

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[23] It certainly does not proceed smoothly. Zelinsky (*Ber.*, **34**, 3801 (1901)) attempted to prepare *bicyclo*[1,2,2]heptanone-7 by pyrolysis of *trans*-hexahydroterephthalic acid and its salts. The main products were apparently benzene and hydrogen; a very small amount of a ketonic fraction was isolated which may have contained some of the desired ketone. It is often assumed that the conversion of dicarboxylic acids to ketones proceeds through $\beta$-keto-acid intermediates, and it may be noted that in the case under discussion, such an intermediate would not be susceptible to decarboxylation. *Cf.* Ketopinic acid, Komppa, *Ber.*, **44**, 1537 (1911).

[24] This argument is not subject to question on the ground that a deep-seated rearrangement similar to that which may be involved in the formation of the santonides (see below) may play a role in the formation of the acetyl lactone, since the latter is hydrolyzed smoothly to the parent dihydrosantonic acid.[3]

[25] Cannizzaro and Valente, *Gazz. chim. ital.*, **8**, 315 (1878); Francesconi, *ibid.*, **25ii**, 471 (1895); Francesconi, *Rend. accad. Lincei*, V, **12ii**, 205 (1903). *Cf.* also ref. 11c.

[26] It may be noted also that both santonic and metasantonic acid give the same diacetyl derivative (XI), as expected, since in this molecule the asymmetry at C.1 is absent. *Cf.* refs. 11c and 25b.

bonate. Then 80 cc. of 5% aqueous potassium permanganate was added slowly, and the reaction mixture was heated gently on the steam-bath for ten to fifteen minutes. The excess permanganate was then destroyed by the addition of 8 cc. of saturated aqueous sulfurous acid, and manganese dioxide was removed by filtration from the still hot solution. The filtrate was chilled, saturated with carbon dioxide, evaporated *in vacuo* at room temperature to a small volume, acidified with sulfuric acid and extracted with ether. Evaporation of the dried (magnesium sulfate) ether extract gave a viscous, light-brown oil, which crystallized on standing in a desiccator for several days. Recrystallization from ether–chloroform gave pure santoric acid, m. p. 181–182°. When the manganese dioxide precipitate was destroyed with sodium bisulfite, and the resulting aqueous solution was worked up as above, a further quantity of the acid was obtained. The total yield of very pure acid was 0.183 g. (16%).

**Santoronic Acid** (*cf.* ref. 11c).—Santoric acid (450 mg.) was dissolved in a little water in a nickel crucible, and 2.0 g. of sodium hydroxide was added. The mixture was taken to dryness on an oil-bath, and then heated to 280° (bath temperature) for fifteen minutes. The mass became hard and swollen before melting to a gray mobile liquid. The cooled, caked fusion mixture was dissolved in boiling water, acidified with sulfuric acid, and extracted with 300 cc. of ether in eight portions. The ether was removed by steam distillation to remove acetic acid, and the aqueous solution was concentrated *in vacuo*, treated with barium hydroxide, and evaporated to dryness. The resulting barium salt was washed with water, and then treated with concentrated hydrochloric acid. The freed acid was extracted from the aqueous solution by ether, and the ether extract concentrated to a small volume. The addition of a few drops of benzene to the well-chilled ether solution brought about the crystallization of santoronic acid, which was recrystallized from ether, m. p. 125–127°; 5 mg. of pure santoronic acid was obtained.

*Anal.* Calcd. for $C_{10}H_{16}O_6$: C, 51.71; H, 6.93. Found: C, 51.69; H, 7.60.

**2,5,6-Tricarbethoxyheptane** (procedures of Cornubert and Borrell[27] and Ruzicka and Steiner[21]).—The Dieckmann condensation with diethyl adipate gave 2-carbethoxycyclopentanone, b. p. 116–119° (25 mm.) in 81% yield. Methylation gave 2-methyl-2-carbethoxycyclopentanone, b. p. 125° (35 mm.) in 85% yield. Diethyl α-methyladipate, b. p. 133–134° (17 mm.) (73%), was obtained on cleavage of the keto-ester; cyclization of the diester gave 1-methyl-3-carbethoxycyclopentanone-2, b. p. 119–121° (25 mm.) in 59% yield. The latter keto-ester was alkylated with ethyl α-bromopropionate; 1-carbethoxy-3-methylcyclopentane-2-one-1-α-propionic acid ethyl ester, b. p. 120–150° (2 mm.), was obtained in 70% yield. Cleavage of this keto-ester gave 2,5,6-tricarbethoxyheptane, b. p. 145–155° (1.5 mm.) in 43% yield. Refractionation of the crude ester (11 g.) gave 9.9 g. of analytically pure triester, b. p. 142–143° (0.2 mm.).

*Anal.* Calcd. for $C_{16}H_{28}O_6$: C, 60.75; H, 8.92. Found: C, 60.70; H, 9.05.

**Hydrolysis of 2,5,6-Tricarbethoxyheptane. A.**—The triester was boiled for twenty-four hours with 20% alcoholic sodium hydroxide solution. Most of the alcohol was then removed and the reaction mixture was neutralized and evaporated to dryness. Extraction of the residue with ether and concentration of the ether solution gave a thick sirup, which could not be induced to crystallize directly. When the sirup was taken up in concentrated hydrochloric acid, and the resulting solution evaporated in a stream of air, crystals separated which were removed, and recrystallized from ether–petroleum ether. The material thus obtained, m. p. 133–134°, was a known isomer of 2,5,6-tricarboxyheptane.[21]

B.—1.4 g. of the triester was boiled for six hours with 25 cc. of concentrated hydrochloric acid. The solution was then evaporated at room temperature, and the brown residue was fused with 4.0 g. of sodium hydroxide at 280° in a nickel crucible. An aqueous solution of the cooled melt was acidified with hydrochloric acid and extracted with ether. The dried ether solution was concentrated and cooled. The crystalline acid (350 mg.) which separated with some viscous material was purified by centrifugation, followed by recrystallization from ether; the 2,5,6-tricarboxyheptane obtained in this way melted at 126–129°; mixed with the isomer of m. p. 133–134° (above), m. m. p. 104–121°.

*Anal.* Calcd. for $C_{10}H_{16}O_6$: C, 51.71; H, 6.93. Found: C, 51.84; H, 7.27.

The 2,5,6-tricarboxyheptane, m. p. 126–129°, mixed with santoronic acid, m. p. 125–127°, from the oxidation of santoric acid (above), had m. m. p. 125.5–127.8°.

**Hydroxy-lactone (XXV, R = H).**—*Apo*santonic acid, m. p. 156–158° was obtained in 22% yield by the method of Wedekind and Jäckh.[15] The acid (0.55 g.) was dissolved in 9 cc. of a chloroform solution of perbenzoic acid[28] (0.535 millimole of perbenzoic acid per cc.). The reaction mixture was kept at 0°. The reaction was followed titrimetrically; one mole of perbenzoic acid was consumed in forty-eight hours. The chloroform solution was then shaken with a small amount of sodium bisulfite solution, to destroy excess perbenzoic acid, and then with cold 10% aqueous sodium bicarbonate, to remove acidic materials. The dried chloroform solution was evaporated and the neutral crystalline product was purified by two recrystallizations from chloroform; 0.43 g. (90%) of the lactone (XXV, R = H), m. p. 193–194.5°, was obtained.

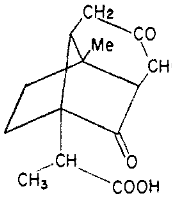
*Anal.* Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.56; H, 8.23.

The lactone (XXV, R = H) (0.1 g.) was heated under reflux in 7.0 cc. of acetic anhydride for four hours. Evaporation *in vacuo* left a heavy oil which crystallized in contact with chloroform and petroleum ether. Recrystallized, the acetyllactone (XXV, R = Ac) had m. p. 160–163°.

*Anal.* Calcd. for $C_{16}H_{22}O_5$: C, 65.26; H, 7.54. Found: C, 65.50; H, 7.24.

## Summary

The structure I for santonic acid is proposed.



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[27] *Bull. soc. chim.*, [4] **47**, 301 (1930).

[28] "Organic Syntheses," Coll. Vol. I, p. 431.