tion yields only anthraquinone. In boiling iso-octane or in carefully dried mineral oil at 140°, 1-bromotriptycene is reduced to triptycene, no ditriptycyl being produced. Ditriptycyldiquinone is not formed by the addition of benzoquinone to 9,9-dianthryl. 1-Aldehydotriptycenequinone was made and its aldehyde group found to be very resistant to oxidation.

The oxidation potential of triptycenequinone is −0.666 v., close to that of hydrindenequinone,

suggesting similar strain in the location of a double bond in the two compounds.

The absorption spectra of triptycene and of 1-bromotriptycene are closely similar. They show fewer maxima than triphenylmethane, and the maxima appear at longer wave lengths and with markedly higher intensities. A kind of cyclopropanic conjugation is proposed for which triptycene is especially favorably constituted.


The Structure of the Santonides

BY R. B. WOODWARD AND E. G. KOVACH

Santonide and parasantonide are isomeric neutral substances of the formula $C_{15}H_{18}O_3$ which were first prepared more than seventy years ago by acetic acid treatment and pyrolysis of santonic acid.[1] The compounds are of more than ordinary interest in view of the complexity of the structural problem which they present and, further, because of their remarkable optical properties (vide infra). With the elucidation of the structure of santonic acid (I) recently in this Laboratory,[2] it became possible for the first time to make a rational approach to the formulation of the santonides.

Since the santonides differ in empirical composition from santonic acid by the elements of a water molecule, it has been assumed generally in the past that they were simple enol-lactones of that acid. It is now readily apparent, however, that this trivial solution of the structural problem is invalid, since (II), and all other enol-lactone structures derived directly from (I), *possess a carbon-carbon double bond in an impossibly strained position.*[3] This view receives decisive support from the fact that on hydrolysis, the santonides are converted not into santonic acid, but into two new isomeric acids, isosantonic acid (from santonide)

and parasantonic acid (from parasantonide). Further, in sharp contrast to santonic acid, which requires very vigorous treatment for transformation to the santonides, the isomeric acids are very smoothly reconvertible to the respective santonides under very mild conditions. 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.

I   II
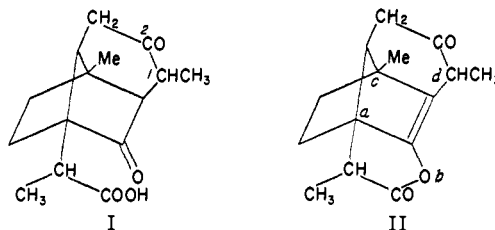
We consider first, and reject, the first of these possibilities. In detail, the only alternative to lactone formation is a loss of water involving the carboxyl group and a hydrogen atom alpha to the C.2 carbonyl group of santonic acid

$$-COOH \qquad HC\overset{|}{\underset{|}{-}}\overset{2}{CO}- \longrightarrow -CO-\overset{|}{\underset{|}{C}}-\overset{2}{CO}-$$
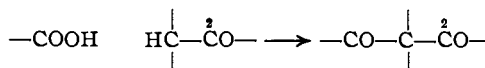
The reaction is not without analogy,[4] and in the case in point would lead to the somewhat, but not greatly, strained structure (III).[5] The necessity for the use of very vigorous conditions in effecting the transformation of santonic acid to the santonides is reminiscent of the circumstances obtaining in the analogous cases. On the other hand, the very facile reconstitution of the santonides from

(1) Cannizzaro and Valente, *Rend. accad. Lincei*, III, **2**, 134, (1878); *Gazz. chim. ital.*, **8**, 309 (1878); Francesconi, *ibid.*, **25**ii, 471 (1895); *Rend. accad. Lincei*, V, **12**,ii, 204, 267, 304 (1903).

(2) Woodward, Brutschy and Baer, THIS JOURNAL, **70**, 4216 (1948).

(3) The four groups *a*, *b*, *c* and *d* attached to a double bond (A) must lie in a common plane if the system is to be strainless. [*Bredt's rule* (Bredt, *Ann.*, **437**, 1 (1924)) follows as a simple corollary from this principle as applied to small bicyclic systems]. It is clear that in (II) (above) the geometry of the molecule necessitates marked deviation from this condition, and that (II) consequently represents a very highly strained molecule. The same conclusion may be reached by noting that (II) contains a *trans*-substituted double bond *within a seven-membered ring*. Finally reference may be made to the recent elegant experimental demonstrations [Prelog, Ruzicka, Barman and Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948); Prelog, Barman and Zimmerman, *ibid.*, **32**, 1284 (1949)] that an unstrained double bond at the bridgehead of a [1,3,*n*] bicyclic system is only possible when *n* ≥ 5; (II) contains a bridgehead double bond in a [1,3,3] bicyclic system. Similar considerations apply to enol-lactone formulas which may be derived from (I) by utilizing the C.2 carbonyl group.

(4) α-Campholonic acid → 2,6-diketocamphane [Miyake and Watanabe, *Proc. Imp. Acad. (Tokyo)*, **11**, 322 (1935); (cf. *C. A.*, **30**, 2949 (1936)]; Komppa and Beckmann, *Ber.*, **69**, 2783 (1936)]; cyclohexanone-3-acetic acid → bicyclo[2,2,2]octane-2,6-dione [Bartlett and Woods, THIS JOURNAL, **62**, 2933 (1940)].
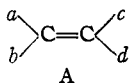
(5) A new *trans* bicyclo[0,3,3]octane system [strain about 7 kc./mole; cf. Barrett and Linstead, *J. Chem. Soc.*, 436 (1935)] would be created in the change. In this respect the reaction would resemble the formation of the keto-anhydride $C_{15}H_{14}O_4$ from santonic acid (cf. ref. 2).
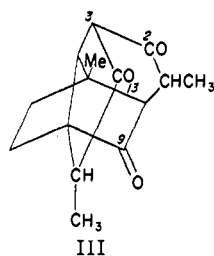
A figure showing a double bond structure appears in footnote 3:

$$\underset{b}{\overset{a}{\diagdown}}C=C\underset{\diagdown d}{\overset{c}{\diagup}}$$

A

III

isosantonic and parasantonic acids points clearly to the lactonic nature of the dehydration products, and must be considered exceptional if the triketone formula be accepted.[6] Beyond that, we have found strong positive evidence of the presence of an enol-lactone group in the santonides: (a) the infrared spectrum of parasantonide possesses a strong band at 5.58 μ, a position characteristic for enol-lactones[7]; (b) the fact that parasantonide is readily attacked by ozone indicates the presence of a carbon–carbon double bond in the molecule. We conclude that the santonides are enol-lactones derived from santonic acid with rearrangement of the carbon skeleton of the latter.

Decisive clarification of the structural position was obtained through the study of the ozonization of parasantonide. When ozone was passed through a chloroform solution of the lactone, the latter was rapidly attacked, and a solid ozonide(s) separated from the solution. When the reaction-mixture obtained by treating the ozonide directly with methanolic hydrogen chloride was chromatographed, four crystalline products were obtained (Table I).

TABLE I

| Compound	M. p., °C.	Composition	Infrared bands, μ
A	100	$C_{13}H_{14}O_4(OCH_3)_4$	5.78
B	117	$C_{15}H_{16}O_4(OCH_3)_2$	5.67 5.78 6.02 6.15
C	137	$C_{15}H_{19}O_4(OCH_3)$	2.80 5.77 5.84
D	155	$C_{15}H_{19}O_4(OCH_3)$	2.80 5.60 5.77

Compound A was identified as tetramethyl β-santorate (IV)[2] by direct comparison with an

IV
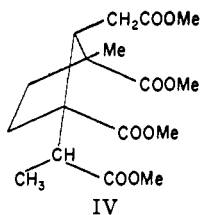
(6) The more so since the cleavage of (III) would have to take place at the C.2-C.3 bond, rather than at C.3-C.13, else iso- and parasantonic acids would simply be stereoisomers of santonic acid, a view incompatible, i. a., with the facts vis-a-vis the conversion of the various acids into the santonides. But the acid obtained by cleavage of C.2-C.3 could undergo normal enol-lactone formation involving the C.9 carbonyl group, and this reaction would certainly be expected to take precedence over β-diketone formation.

(7) Cf. "Spectrographic and Synthetic Studies on the Structure of Penicillin G" (Progress Reports under Contract OEMcmr-445 with the Committee on Medical Research of the O. S. R. D., 1944-1945) by the Shell Development Group (Emeryville, California); Whiffen and Thompson, J. Chem. Soc., 1008 (1946); Woodward and Singh, THIS JOURNAL, 71, 758 (1949).

authentic sample. This result is of primary importance in the structural argument, since it enables us to place thirteen of the fifteen carbon atoms of parasantonide, and, taken with the presence in the latter of an enol-lactone group permits only one of the structures (V), (VI), (VII) or (VIII) for that molecule.

V

VI

VII   VIII
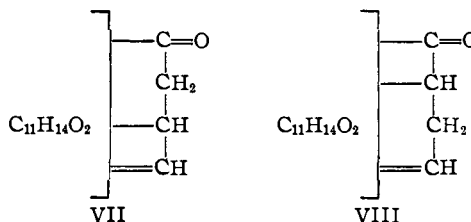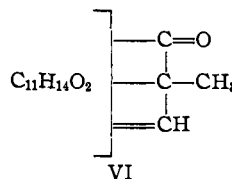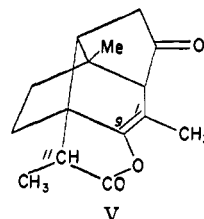
Consideration of the properties of compound B permits an unequivocal choice between the alternative formulas (V)–(VIII). Thus, the presence in the infrared spectrum of B of bands at 6.02 and 6.15 μ is clearly indicative of the presence in the molecule of the β-diketone enol ether system (XI)[8]; confirmation of this view was obtained
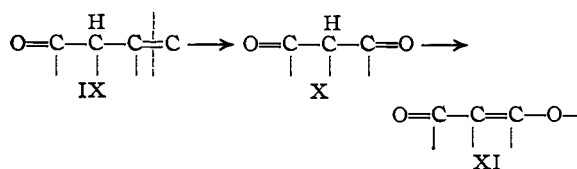

through the observation that the ultraviolet spectrum (Fig. 1) of compound B possessed a band (λmax 268 mμ, log ε = 4.10) characteristic for the system (XI).[8] Clearly the grouping (XI) arises from (IX) through oxidative scission of the double bond, enolization and methylation; since the system (IX) is contained within the structure (V) and not within (VI)–(VIII), we conclude that parasantonide possesses the structure (V).

Though the remaining details of the structure of compound B are not definitive with respect to

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(8) The infrared and ultraviolet spectral characteristics of the system XI were determined through measurements made in this Laboratory on dimedon methyl ether, on 3- and 4-methoxytoluquinones, on adducts from these quinones with certain dienes, and on reduction products from the adducts (Woodward, Stork, Wineman, Nelson and Bothner-By, to be published).

the main structural argument, it is worthy of note that a plausible complete formulation is readily constructed. The infrared spectrum reveals the presence of an ester group (5.78μ)[9] and a *saturated* five-membered lactone group (5.67μ).[7,10] The genesis of these groups may be envisaged as involving the attack of a cationoid peroxide oxygen atom of an ozonide (XII) upon the spacially proximate anionoid C.3 (as enol); the complete change (XII, arrows) leads through (XIII) to the

XII   XIII
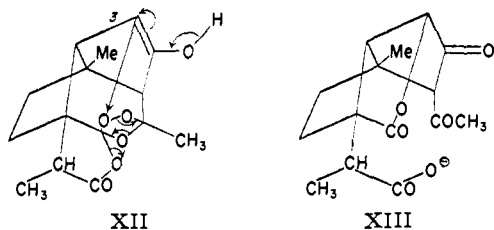
full structure (XIV), which is in all respects a satisfactory expression for compound B.[11]

XIV
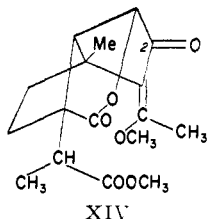
The ozonization products C and D are also readily formulable in terms of the structure (V) for parasantonide. If the primary ozonide from the latter is of the type (XV),[12] its decomposition may be expected to lead, in part, to substances containing

XV   XVI
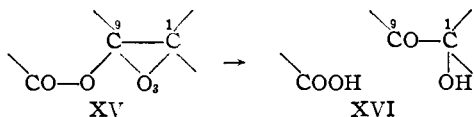
ing the part structure (XVI).[13] In the case at hand, then, decomposition by methanolic hydrogen chloride may lead to the normal (XVII, R = CH₃) and *pseudo* (XVIII) esters of the keto-acid (XVII, R = H). The properties of compounds C and D are in excellent accord with the view that these substances possess structures (XVII, R = CH₃) and (XVIII), respectively. Thus, the infrared spectrum of C has a band at 5.77 μ, corresponding to the ester[9] and five-ring[9] carbonyl

(9) Cf. Jones, Williams, Whalen and Dobriner, THIS JOURNAL, 70 2024 (1948).

(10) Dr. G. Singh of this Laboratory has found the lactone carbonyl band of butyrolactone to be at 5.68μ, a value very close to those found for a number of saturated five-membered lactones by the Shell workers (ref. 7).

(11) The available information does not permit a choice between the isomeric enol ethers containing O=²C—C=C—OCH₃ (as in XIV) and CH₃O—²C=C—C=O.

(12) Cf. Long, Chem. Revs., 27, 437 (1940).

(13) Alternately, the same result may be achieved if the ozone is simply acting as an oxidizing agent which acts as a source of OH⁺, or an equivalent, which attacks C.1.
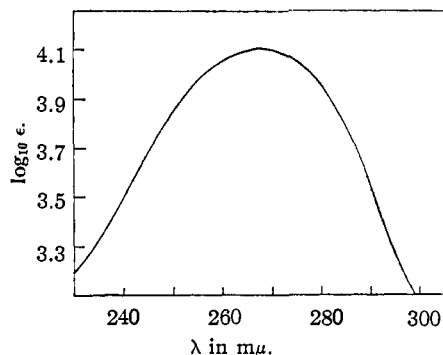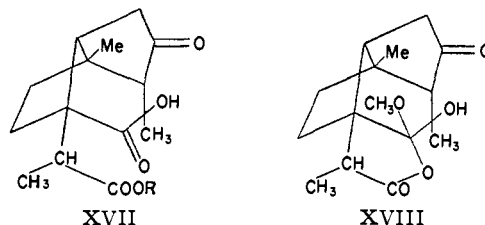
Fig. 1.—Ultraviolet spectrum of compound B in ethyl alcohol.

groups of (XVII), and another at 5.84 μ, attributable to the six-ring carbonyl group.[9] In D, the band for the five-ring carbonyl group (5.77 μ) persists, but, as required by (XVIII), the six-ring

XVII   XVIII

carbonyl band is replaced by a band at 5.60 μ, the expected position for a five-membered acetal–lactone carbonyl group.[14] The spectrum of each of the compounds possesses a band at 2.8μ, in accord with the presence of hydroxyl groups in the structures proposed. Further support for these views was forthcoming when it was found that *both C and D were hydrolyzed by dilute aqueous acid to the same acid*, $C_{15}H_{20}O_5$, which may be formulated as (XVII, R = H).

It will be observed that two stereoisomers of the structure (V) differing in configuration at C.11 are possible. Parasantonide is one of the isomers, and the isolation of methyl β-santorate from the degradation of the lactone indicates that it possesses a configuration at C.11 opposite to that which obtains at the corresponding center in the precursor, santonic acid (I). There is no doubt that santonide is the other possible diastereomer of the structure (V), since we have been able to obtain an equilibrium mixture of methyl isosantonate (XIX, R = CH₃) and methyl parasantonate (XX, R = CH₃) by treatment of a pure sample of the latter in hot methanol with catalytic quantities of sodium methoxide (in-

(14) The group–OR in the γ-position of a γ-lactone will be expected to shift the carbonyl absorption to slightly shorter wave lengths as compared with that of the unsubstituted compounds (5.67μ), through increasing the double bond character of the carbonyl group (cf. CH₃O—C—O—C— ↔ CH₃O⊖ C=O—C—).

version through —C=C (with 11, O⊖, OCH₃, CH₃ groups). Two additional stereoisomers of the acids (XIX *or* XX, R = H)
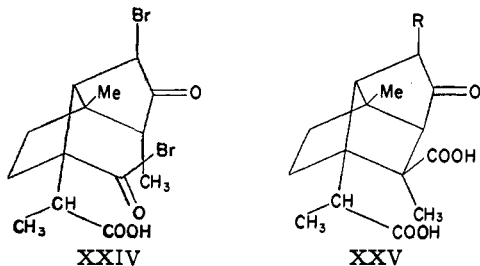
XIX

XX
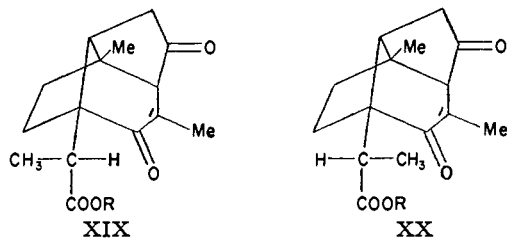
are theoretically possible (inversion at C.1) but no evidence of the existence of such isomers has been forthcoming in our work, or in that of earlier investigators. It is not unreasonable to suppose that the methyl group at C.1 assumes a stable configuration strongly favored for steric reasons when asymmetry is created at C.1 during the hydrolysis of the lactones (V).

In the course of the early investigations on the santonides, the Italian school discovered[1] a number of transformations of parasantonide and parasantonic acid, most of which are readily interpretable on the basis of the structures (V) and (XIX, R = H). Thus, parasantonide imide is (XXI, R = H) (*cf.* the formation of the anhydroamide (XXIII) from the enol-lactone (XXII) of pulegone acetic acid[15]). Dibromoparasantonic
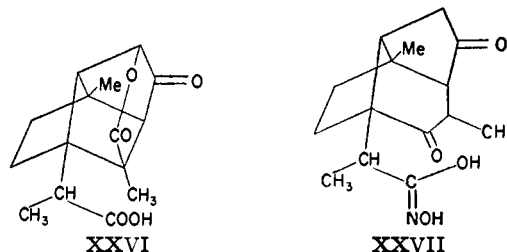
XXI

XXII

XXIII
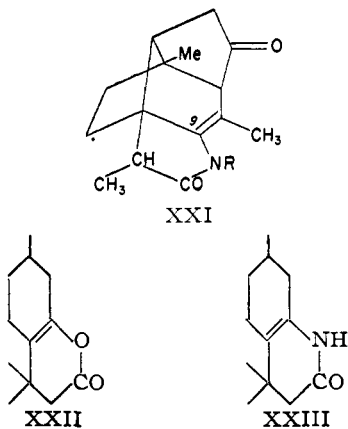
acid may be formulated as (XXIV), and dioxyparasantonic acid as (XXV, R = OH) (*cf.*

XXIV

XXV

chlorocyclohexanone → cyclopentanecarboxylic acid, *etc.*[16]); dehydrodioxyparasantonic acid then becomes (XXVI), and the chloro-acid $C_{15}H_{11}O_5Cl$, (XXV, R = Cl). Parasantonhydroxamic acid (XXVII) is readily formulable, as is parasantonide oximide (XXI, R = OH).

XXVI

XXVII

It may be suggested that the transformation of the latter to oxyparasantonide imide involves a rearrangement of the type -N(OH)C=C- → -N=C-C(OH)- (*cf.* phenylhydroxylamine → *p*-aminophenol[17]) leading to (XXVIII); in that event, oxyparasantonic acid becomes a stereoisomer of compound C (XVII). It must be emphasized that
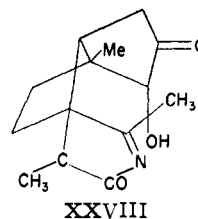
XXVIII

the structures (XXIV) through (XXVIII) cannot be considered definitive in the absence of further experiments specifically designed to test the hypotheses implied by the formulas written; in several cases equally plausible alternatives are possible, and the expressions are presented here solely in order to show that the known chemistry of the santonides offers no barrier to the acceptance of the structures (V) and (XIX, R = H).

We turn now to a consideration of the mechanism by which the santonides are formed from santonic acid. We observe first that a simple interchange of groups attached to contiguous atoms by either of two processes (XXIX, arrows) or (XXX, arrows) serves to transform the san-

XXIX

XXX

(15) Vorländer, *Ann.*, **345**, 196 (1906).
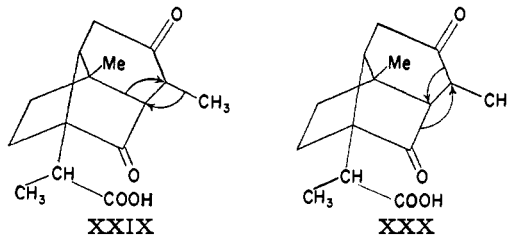
(16) Favorski and Bozhovski, *J. Russ. Phys.-Chem. Soc.*, **46**, 1098 (1915).

(17) Bamberger, *Ber.*, **27**, 1349, 1552 (1894).

tonic acid skeleton into that of parasantonic acid. It is most unlikely, however, that the bonds involved in one of the purely formal schemes shown simply break and reform anew in a different fashion. In order to account for the change in terms of electronic processes for which analogy is available, we suggest the changes symbolized by the expressions (XXXI) through (XXXIII).

I →

XXXI

XXXIII ← XXXII

↓

V
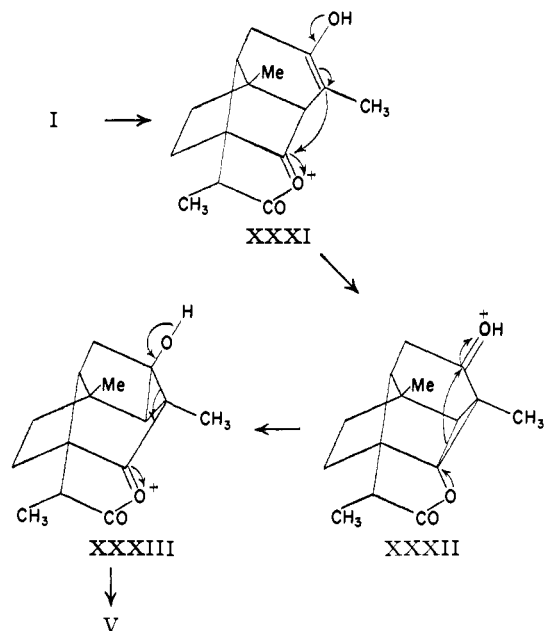
The utilization of a path involving (quasi[18]) three-membered ring intermediates may be considered unusual, but it will be recalled that in other somewhat analogously constituted rigid systems, isolable three-membered ring compounds (cf. tricyclene, i-cholesterol) are very readily formed.

We conclude with some comments on the remarkable optical properties of the santonides and some related compounds. Those compounds in which the carboxyl group is involved in ring formation have very high optical rotatory power, while the corresponding open compounds have normal (relatively) low specific rotations (Table II).

TABLE II

	$[\alpha]_D$
Santonide	+ 758[a]
Parasantonide	+ 897[a]
Parasantonide imide	+1135[b]
Parasantonide oximide	+ 999[b]
Isosantonic acid	− 74[b]
Parasantonic acid	− 98[a,b]

[a] Nasini, Gazz. chim. ital., 13, 151(1883); Carnelutti and Nasini, Ber., 13, 2210 (1880). [b] Francesconi, ref. 1.

(18) In intermediates such as those postulated, the making and breaking of the various carbon–carbon bonds involved will be concerted processes; consequently none of the bonds of the three membered rings in the expressions above can be considered normal cyclopropane ring bonds.

Analogous circumstances obtain in connection with the ultraviolet absorption characteristics of these substances. Methyl parasantonate, like santonic acid, exhibits normal low intensity absorption (log ϵ = 1.88) at 293 mμ (Fig. 2), of the type characteristic of the isolated carbonyl group. The ultraviolet spectrum of parasan-
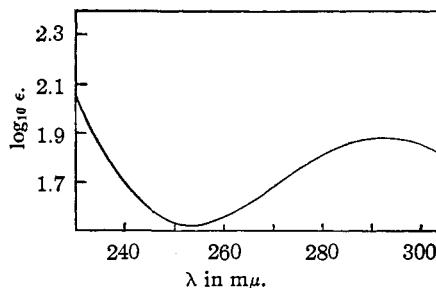

Fig. 2.—Ultraviolet spectrum of methyl parasantonate in ethyl alcohol.

tonide is sui generis.[19] The very high intensity of the band at 300 mμ is without parallel among other known carbonyl compounds, yet no group other than a carbonyl group is present within the parasantonide molecule with whose electronic transitions the band could normally be associated. Mitchell and Schwarzwald[19] have measured the rotatory dispersion of parasantonide through the 300 mμ band (α max = ca. ± 32,000°) and have shown beyond question that it is the electronic system responsible for that band which makes the major contribution to the optical rotation of the molecule. In short, the high rotation and the abnormally high carbonyl absorption intensity have a common basis. We should like to point out that in (V) the carbonyl group moment and the very high electric moment of the lactone group are held very rigidly in a particular orientation one to another, and that in the corresponding open compounds this relationship disappears. So far as we are aware the fundamental theory of absorption intensities is insufficiently far advanced to permit assessment of the significance of that or other structural relationships in the molecule of parasantonide for the unusual optical characteristics of the substance.

Experimental

Parasantonide.—(Cf. refs. 1b and 19b.) Considerable difficulty was encountered in early attempts to prepare the lactone. The duration and temperature of the pyrolysis, the mode of distillation, and the details of purifying the distillate were studied at length. The process described below is reproducible, and has consistently given yields in the neighborhood of 20%.

Fifty grams of santonic acid was refluxed for seven hours in 250 cc. of glacial acetic acid. The solution was divided into batches of 30–40 cc., which were pyrolyzed separately. A batch was placed in a 50-cc. modified Claisen flask fitted with a capillary bubbler; the side arm of the flask was sealed to a vertical 15-cm. test-tube, about 5 cm. be-

(19) Mitchell and Schwarzwald, J. Chem. Soc., 889 (1939); cf. also Mitchell and Scott, ibid., 686 (1947). We have confirmed the previous measurements of the ultraviolet spectrum of parasantonide.

low the lip. The system could be evacuated through the mouth of the test-tube receiver, either with a water aspirator or with a vacuum pump. The flask was placed in a Wood's metal-bath, whose temperature could be readily controlled, and a slow stream of pure, dry nitrogen was passed through the flask during the entire pyrolysis. The bath was set at about 100°, and a low vacuum applied (barely enough to distil the acetic acid) while the bath was gradually heated to 200–220°. At this point the vacuum was removed, and the bath heated to 290–300° and maintained at that temperature for three to four hours. The acetic acid was pipetted out of the receiver, which could be rinsed with ether. Finally, the bath temperature was reduced to 200° and the pressure reduced to 2–3 mm. Raising the temperature slowly gave first a light yellow oily distillate, which became dark reddish-brown as the distillation temperature rose. Distillation was halted at 300°. The distillate quickly set to a gum, which was dissolved by rinsing the receiver with several portions of ether, which were combined in a separatory funnel. The remaining batches were treated in a like manner, and the combined ethereal solutions washed repeatedly with 5% sodium carbonate solution until the wash solution remained colorless. This took as many as thirty or forty washings, but unless all acidic impurities were removed in this manner, the parasantonide crystallized with extreme difficulty or not at all. After this thorough washing, the ether solution was dried over anhydrous sodium sulfate and evaporated at or below room temperature. Parasantonide crystallized in small white rhombic crystals, m. p. 108–110°; $[\alpha]D$ +890°; yield 10.8 g. (21.6%).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.17; H, 7.36. Found: C, 73.24; H, 7.60.

It seems necessary to carry out the pyrolysis on amounts not greater than 10 g. of santonic acid. Experiments using larger portions invariably gave very low yields. Parasantonide was also obtained without refluxing santonic acid in glacial acetic acid. In this method, solid santonic acid was placed in the distilling flask and simply heated to 300°, under nitrogen, for three or four hours. Distillation and purification was the same as described above, but the yield in this method was rarely greater than 10%.

In several runs, the distillation product, even when carefully separated from all acidic impurities, crystallized only partially or not at all. It was possible to obtain a higher yield by converting this oil to methyl parasantonate. The oil was simply dissolved in about five times
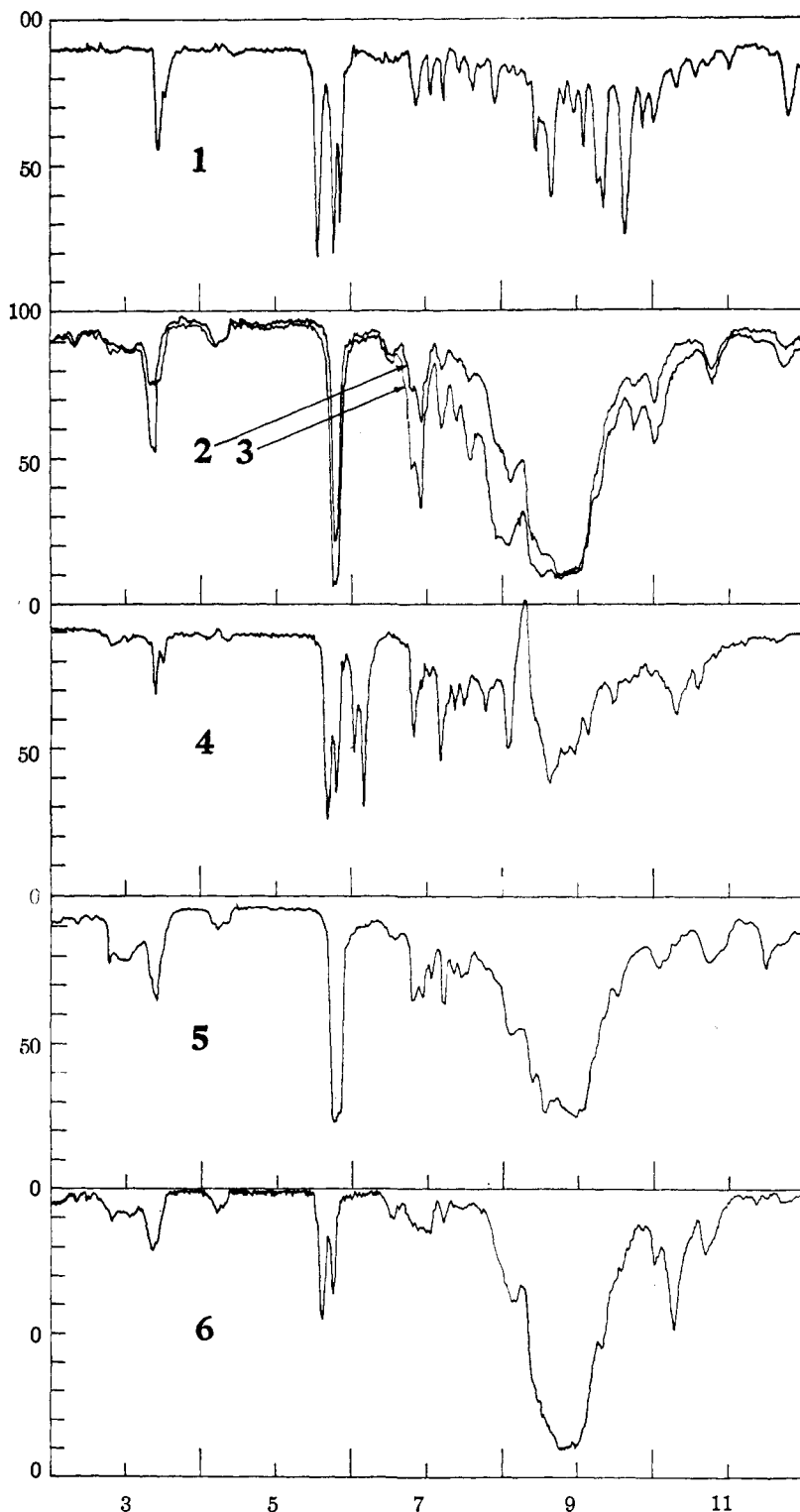
Fig. 3.—Infrared spectra in chloroform: (1) parasantonide V; (2) tetramethyl β-santorate (IV, R = H); (3) compound A (IV, R = H); (4) compound B (XIV); (5) compound C (XVII, R = Me); (6) compound D (XVIII).

its volume of absolute methanol, treated with a few drops of concentrated hydrochloric acid, and warmed on the steam-bath for ten minutes. Cooling the solution in an ice–salt mixture, and scratching, gave a crystalline precipitate which could be filtered off and purified by washing with methanol or by recrystallizing from methanol and water. The yield of methyl parasantonate obtained by this method was ca. 30% (based on santonic acid), m. p. 184–186°. The ester can be hydrolyzed to parasantonic acid and this, in turn, may be dehydrated to yield parasantonide (vide infra).

Parasantonic Acid. A. From Parasantonide.—One gram of parasantonide was warmed on the steam-bath with 20 cc. of 10% potassium hydroxide solution for twenty minutes. The solid material dissolved within five minutes. Chilling, followed by acidification with 2 N hydrochloric acid yielded a crystalline precipitate which was filtered off, dried and recrystallized from ether; yield 0.9 g. (90%), m. p. 177–178°. (The literature[1] reports the melting point of parasantonic acid as 169–170°, but all samples prepared in this Laboratory melted over 175°.)

B. From Methyl Parasantonate.—One gram of methyl parasantonate was heated on the steam-bath for one hour with 30 cc. of 20% potassium hydroxide solution. The solid material dissolved within twenty minutes. Chilling, followed by acidification with 2 N hydrochloric acid produced a small amount of a crystalline precipitate. The aqueous solution was extracted four times with 20-cc. portions of ether which were collected, dried (sodium sulfate), and concentrated. Parasantonic acid crystallized in small white crystals; yield 0.88 g. (88%).

Parasantonide from Parasantonic Acid.—Parasantonic acid (0.8 g.) was dissolved in 10 cc. of acetic anhydride and heated under reflux for thirty minutes. The acetic anhydride was removed under water-pump pressure and the residue taken up in ether, which was washed with 5% sodium carbonate solution, dried over calcium chloride, and evaporated at room temperature. The yield of parasantonide was 0.62 g. (77%), m. p. 108–109°.

Methyl santonate was prepared essentially according to the procedure of Harries and Stähler.[20] The yield of the crude ester from 7 g. of santonic acid was 4.5 g. (64%), and it had a melting point of 65–70°. A single recrystallization from methanol raised the melting point to 84–85°.

Methyl Parasantonate.—Ten cc. of a 40% potassium hydroxide solution was covered with 30 cc. of ether, and about one gram of N-nitrosomethylurea was added in small amounts, at 0–5°. The diazomethane which was produced went into solution in the ether layer, and this was decanted into an ethereal solution of 1.0 g. of parasantonic acid. There was a rapid reaction, as evidenced by the evolution of nitrogen, and the diazomethane solution was added until its yellow color persisted. Excess diazomethane was removed by taking the solution to dryness on the steam-bath, and the residual oil was crystallized from dry ether. The ester[1b] separated in flat plates, m. p. 185–186°; yield 0.92 g. (91%).

Metasantonic Acid.[1b,1c]—Ten grams of santonic acid was dissolved in 40 cc. of acetic anhydride and then 20 g. of solid sodium acetate was added. Refluxing for seven hours caused all material to go into solution. The acetic anhydride was removed in vacuo, and the residue taken up in 5% sodium carbonate solution which was extracted several times with ether. Drying and concentrating the ether extracts gave crystals of diacetylsantonic acid; m. p. 204–206°; yield 0.7 g. (6.5%).

A solution of 0.7 g. of diacetylsantonic acid in 15 cc. of 10% potassium hydroxide solution was heated on the steam-bath for one hour. The solution was filtered and acidified with 2 N hydrochloric acid. No precipitate formed but extraction with ether, which was dried and concentrated, yielded crystals, m. p. 164–166°. A mixed melting point with pure santonic acid gave a depression, 142–154°.

Methyl Metasantonate.[1b]—A solution of 0.15 g. of metasantonic acid in 2 cc. of methanol was treated with two drops of concentrated sulfuric acid and refluxed for three hours. Most of the methanol was removed by evapo-

(20) Harries and Stähler; Ber., **37**, 260 (1907).

ration, and the residue taken up in ether which was washed with 5% sodium carbonate solution until all acidic material was removed. Drying of the ether (potassium carbonate) and evaporation yielded crystals; m. p. 96–98°, yield 0.05 g. (33%).

Isomerization of Methyl Santonate to Methyl Metasantonate.—A solution of 3.0 g. of methyl santonate in 65 cc. of absolute methanol was treated with 0.025 g. of sodium, and after the sodium had reacted the mixture was refluxed for forty-eight hours. About 55 cc. of the methanol was distilled off, and the solution was adjusted to pH 4 with dilute hydrochloric acid. It was then taken up in ether and washed three times with water and then three times with 5% sodium carbonate solution. After drying over potassium carbonate, the ether was evaporated. After standing overnight the residual oil deposited crystals which were extraordinarily soluble in methanol. Recrystallized from methanol, they had m. p. 82–84°, and showed no depression with pure methyl santonate. The remaining oil was chromatographed as follows: a 1.0 × 12.0 cm. column of Alcoa, Grade F-20 Alumina was formed with low boiling (30–60°) petroleum ether. The oil was poured onto the column in 5 cc. of solution A, below, and the column was washed successively with 10-cc. portions of solutions A–J, and arbitrary cuts of 5–10 cc. taken from the bottom of the column (18 cuts in all). The

Solutions	% Pet. ether	% Benzene	% Ether	% Methanol
A	60	40		
B	42	58		
C	21	79		
D		100		
E		50	50	
F		25	75	
G			100	
H			75	25
I			50	50
J				100

solvents were allowed to evaporate at room temperature. Crystals were found in cut 14, with a very sharp melting point of 100–100.5°. A mixed melting point with authentic methyl metasantonate showed no depression.

Isomerization of Methyl Parasantonate to Methyl Isosantonate.—A solution of 1.5 g. of methyl parasantonate in 40 cc. of absolute methanol was treated with 0.04 g. of sodium and after the sodium had reacted the mixture was heated under reflux for seven days. Most of the methanol was removed by distillation, and the residue was made barely acid with dilute hydrochloric acid. The entire solution was taken up in ether which was washed with 5% sodium carbonate solution to remove any hydrolyzed ester, and the ethereal solution was dried over anhydrous potassium carbonate and concentrated by evaporation. About 0.5 g. of the unchanged methyl parasantonate crystallized out, leaving a viscous oil. This was chromatographed as follows. A 14-cm. column was formed of fifteen grams of Alcoa Grade F-20 Alumina, using petroleum ether (boiling range 30–60°) to form the column. The oil was poured on the column in 10 cc. of a mixture of 60% petroleum ether and 40% benzene. It was then washed successively with 10-cc. portions of the following solutions.

Solution	% Pet. ether	% Benzene	% Ether	% Methanol
A	60	40		
B	40	60		
C	10	90		
D		80	20	
E		50	50	
F		30	70	
G			100	
H			70	30
I			50	50
J				100

As the solvents dripped through the tube, arbitrary cuts of 3–5 cc. were taken, a total of thirty-six in all. Evaporation of the solvent showed that cuts 1–8 and 24–36 were empty, cuts 9–16 gave crystals with m. p. 70–78°, and cuts 19–23 gave crystals with m. p. 181–183°. This last product was methyl parasantonide, as shown by mixed melting point determination, but there was a new substance in the forerun. Cuts 9–16 were taken up in 10 cc. of a 50/50 mixture of benzene and petroleum ether and recycled through a new 1.0 × 17 cm. column of 8.5 g. of alumina. Only the 50/50 mixture was used as a developer and eluent, and fifteen 2–3-cc. cuts were collected. Evaporation of the solvent gave crystals with m. p. 72–73°, which were presumably methyl isosantonate (reported[16], m. p. 69–70°).

Ozonization of Parasantonide.—Three and one-half grams of parasantonide was dissolved in 80 cc. of dry carbon tetrachloride and treated with 2–6% ozone for five hours at −5 to −10°. A light yellow ozonide precipitated. The carbon tetrachloride was removed *in vacuo* at room temperature, and the oily residue taken up in 50 cc. of absolute methanol. This was treated with dry hydrogen chloride for twenty minutes, using an ice-bath to cool the reaction mixture. The latter was then evaporated *in vacuo*, and the residual oil was dissolved in ether and separated into acidic and neutral fractions with 5% sodium carbonate solution. The alkaline solution was acidified with 2 N hydrochloric acid and extracted several times with ether. Both ether solutions were dried over anhydrous sodium sulfate, and concentrated to oils.

Neutral Fraction.—The neutral oil, in 10 cc. of benzene, was poured on a 1 × 32 cm. column of Alcoa, Grade F-20 Alumina and washed with 250 cc. of a mixture of 80% benzene and 20% ether, and then with 300 cc. of ether. The eluents were pulled through the column with a gentle suction, and nine cuts taken of 50 cc. each. Evaporation of the solvent gave a heavy oil in cuts 1–2, and crystals in cuts 3–9, which collected and recrystallized from ether and petroleum ether, weighed 160 mg., and had a melting point of 135–137° (Compound C).

Anal. Calcd. for $C_{15}H_{19}O_4$-OCH_3: C, 65.30; H, 7.48; -OCH_3, 10.28. Found: C, 65.00; H, 7.44; -OCH_3, 11.06.

The oil from cuts 1–2 was put on a fresh 1 × 22 cm. column and washed with 100 cc. of the 80–20% mixture and 35 cc. of ether. Twenty-seven 5-cc. cuts were taken and evaporated to oils. Standing overnight and scratching produced crystals in 11–27. These were collected and recrystallized from ether–petroleum ether, to give 53 mg. of compound D m. p. 154–155°.

Anal. Calcd. for $C_{15}H_{19}O_4$-OCH_3: C, 65.30; H, 7.48; -OCH_3, 10.28. Found: C, 65.27; H, 7.42; -OCH_3, 10.82.

The oils from cuts 1–10 above were recycled on a fresh 1 × 15 cm. column and washed with 100 cc. of 90% benzene–10% ether and then with 25 cc. of ether. Twenty-five 5-cc. cuts were taken, and scratching of the residual oils

produced crystals in cuts 6–19. Collection and recrystallization gave 24.5 mg. of compound B, m. p. 115–117°.

Anal. Calcd. for $C_{15}H_{18}O_4$=2-OCH_3: C, 63.34; H, 6.88; 2-OCH_3, 19.28. Found: C, 63.20, 62.57; H, 6.80, 6.90; 2-OCH_3, 20.61.

Acidic Fraction.—The acidic oil from the ozonization was taken up in ether and methylated with diazomethane according to the method of "Organic Syntheses," Coll. Vol. I, p. 165. The neutral oil, in 10 cc. of benzene, was put on a 1 × 20 cm. Alumina column and washed with 250 cc. of 80% benzene–20% ether and then with 50 cc. of ether. Thirty cuts of 10 cc. each were taken, and upon concentration cuts 16–30 gave crystals, m. p. 99–100°; yield 162 mg.; mixed melting point with tetramethyl β-santorate, 98–99°.

Anal. Calcd. for $C_{13}H_{14}O_4$-4-OCH_3: C, 57.04; H, 7.29; 4-OCH_3, 34.6. Found: C, 57.09; H, 7.29; 4-OCH_3, 36.21.

An authentic sample of tetramethyl-β-santorate, m. p. 98–100°, was prepared through β-santoric dianhydride by the method of Francesconi.[21] The infrared spectrum of the authentic ester was identical with that of the ozonization product. Infrared spectra of parasantonide, and of the ozonization products are shown in Fig. 3.

Hydrolysis of Compounds C and D.—Normal alkaline hydrolysis of the ozonization products melting at 137 and 155° gave unmanageable products, so hydrolysis with dilute acid was employed. Fifty mg. of each ester, treated separately, was taken to dryness on the steam-bath from solution in 10 cc. of 2 N hydrochloric acid (ten hours). The light yellow product in each case crystallized well from a mixture of ethyl acetate (very soluble) and dry ether (almost completely insoluble). The melting point of the hydrolysis product of the 137° compound was 174–175°, and that obtained from the 155° compound, 173–175°. Admixture of the two samples gave no depression, m. m. p 173–175°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.53; H, 7.42.

Summary

The structure I for parasantonide is proposed.

I
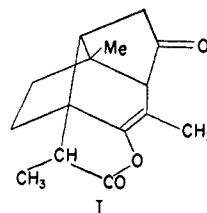
(21) Francesconi, *Gazz. chim. ital.*, **22**, 181 (1892).