[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

Acid-catalyzed Transformations of ψ-Santonin[1]

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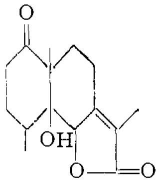
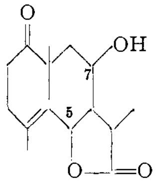
When ψ-santonin is treated with 6 N hydrochloric acid, the lactonic hydroxyl group is eliminated and 1-keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid (IV) (ψ-santonic acid) is formed. This acid, upon heating, is transformed into a lactone with concomitant migration of the conjugated diene system and 1-keto -$\Delta^{2,4(10)}$-santadien-12,7-olide (XI) is obtained. When ψ-santonin is treated with 55% sulfuric acid a more extensive rearrangement occurs and the desmotropo-ψ-santonins which are formed possess structure XV.

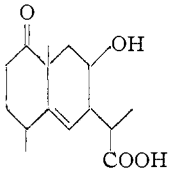
The sesquiterpenic acid lactone, ψ-santonin ($C_{15}H_{20}O_4$), has been studied extensively by Cocker and on the basis of his results structure I was postulated. As a consequence of some recent work in this Laboratory[1,4,5] an alternate structure II has[3] been assigned to the compound and this formulation differs from that originally postulated by the former workers[3] in the location of the double bond and the free hydroxyl group. Such a reassignment was found necessary in order to account for many of the transformations in the ψ-santonin series. Recently, using different evidence, Cocker and his co-workers[6] have concurred with this new formulation. In continuing our study of this sesquiterpenic acid lactone, some of the interesting reactions it undergoes upon treatment with acid have been reinvestigated and interpreted on the basis of the new structure II.



I



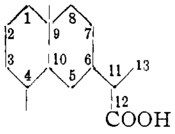
II



III

When ψ-santonin is allowed to react with dilute hydrochloric acid at room temperature,[7,8] an acidic material, ψ-santonic acid ($C_{15}H_{20}O_4$), is formed and when the acid treatment is concentrated sulfuric acid at 50°,[7,9,10] two isomeric phenolic lactones, (+)-β-desmotropo-ψ-santonin and (+)-α-isodesmotropo-ψ-santonin ($C_{15}H_{18}O_3$), are obtained. Furthermore, when ψ-santonic acid is treated under the latter conditions,[7] it also is transformed into (+)-β-desmotropo-ψ-santonin.

With regard to the structure of ψ-santonic acid, it has been shown that the basic carbon skeleton of ψ-santonin has not undergone rearrangement, since a tetrahydro-ψ-santonic acid upon Clemmensen reduction followed by selenium dehydrogenation[8] gives rise to 1-methyl-7-ethylnaphthalene. This latter hydrocarbon also is obtained from 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid[9,10,11] (III), a



(a)

compound which is transformed readily into ψ-santonin.[5] ψ-Santonic acid possesses two ethylenic double bonds, a carbonyl group with an adjacent methylene and a hydroxy group. The ultraviolet spectrum of the acid shows an intense maximum at 234.5 mμ (ε 15,000); Cocker and Lipman[8] interpreted this spectrum as that of a disubstituted α,β-unsaturated ketone and suggested that the two olefinic linkages were not in conjugation. Such structural characteristics were difficult to reconcile with any compound derived from structure II and so attention was directed toward the nature of the chromophoric system and the groupings lost in the formation of the new unsaturated linkage in the acid.

ψ-Santonin possesses two possible sources of this new olefinic bond, the free hydroxyl at C_7 and the allylic lactonic oxygen function at C_5. The first can be ruled out since it has been shown that 1-keto-7-hydroxy-$\Delta^{5(10)}$-santenic acid (III), a compound possessing the original C_7-hydroxyl,[1] is stable to acid under conditions which rearrange ψ-santonin.[9] Thus, it must be concluded that ψ-santonic acid is formed by conversion of the γ-lactone of ψ-santonin to an unsaturated acid. That this new double bond is in conjugation with the original unsaturated linkage was established readily from the spectrum of the acid. It was found that ψ-santonic acid showed bands in the infrared (oil mull) at 1707 cm.$^{-1}$, characteristic of a saturated six-membered ring ketone,[12] and at 1605 and 1570 cm.$^{-1}$, characteristic of a conjugated diene system.[12] A conjugated unsaturated ketone, such as was postulated by Cocker and Lipman,[8] on the other hand, would be expected to absorb at 1665 cm.$^{-1}$.[12] The presence of an isolated ketone was established further by examination of the ultraviolet spectrum of the 2,4-dinitrophenylhydrazone of the acid. It was found that this derivative retained the characteristic 234.5 mμ band which now must be attributed to a conjugated diene and, in addi-

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[1] For the preceding paper in this series see THIS JOURNAL, **77**, 2451 (1955).

[2] Recipient of the Dow Fellowship in Chemistry, Univ. of Calif., 1953–1954.

[3] W. Cocker, B. E. Cross and D. H. Hayes, *Chemistry and Industry*, 314 (1954), and earlier papers.

[4] W. G. Dauben and P. D. Hance, THIS JOURNAL, **75**, 3352 (1953).

[5] W. G. Dauben and P. D. Hance, *ibid.*, **77**, 606 (1955).

[6] N. M. Chopra, W. Cocker and J. T. Edwards, *Chemistry and Industry*, 1535 (1954); W. Cocker, *ibid.*, 19 (1955).

[7] W. Cocker, B. E. Cross and C. Lipman, *J. Chem. Soc.*, 959 (1949).

[8] W. Cocker and C. Lipman, *ibid.*, 1170 (1949).

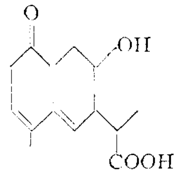
[9] G. R. Clemo and W. Cocker, *ibid.*, 30 (1946).

[10] W. Cocker and C. Lipman, *ibid.*, 533 (1947).

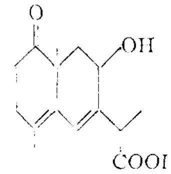
[11] This nomenclature is discussed in reference 4 and is based upon the hypothetical nucleus, santanic acid (a).

[12] R. N. Jones, D. Humphries, E. Packard and K. Dobriner, THIS JOURNAL, **72**, 86 (1950).

tion, the material displayed a new band at 360 mμ, characteristic of a saturated ketone 2,4-dinitrophenylhydrazone.[13] The chemical and spectral features allow either structure IV or V to be assigned to ψ-santonic acid. The choice between these two structures rests on the following considerations. First, employing the diene rules of Fieser,[14] the calculated absorption for IV would be 239 mμ and for V would be 244 mμ as compared to the experimental value of 234.5 mμ. Second, V is an allylic alcohol and should be susceptible to oxidation by MnO_2 to yield a conjugated dienone.[15] Although no crystalline material could be isolated, examination of the spectrum of the reaction mixture during the course of the attempted oxidation did not show the presence of any absorption at 314 mμ where such a dienone would be expected to absorb. Thirdly, it has been reported by Cocker and Lipman[7] that when ψ-santonic acid is allowed to stand for 7 days at room temperature with 8% sodium hydroxide, an isomeric compound is formed. It now has been found that this new compound, which is difficult to isolate in pure form, possesses an absorption maximum at 330 mμ, a value suggestive of a homoannular dienone. (The spectral characteristics of such a system are discussed below.) Such a transformation would be expected of a β,γ,δ,ε-dienone, whereas the system which is present in V would not be expected to migrate under such conditions. On the basis of such evidence it is strongly suggestive that IV best represents the structure of ψ-santonic acid and this material should be designated 1-keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid.

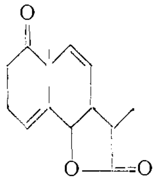


IV

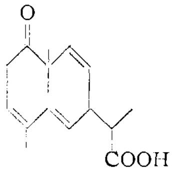


V

Further evidence for the formation of a $\Delta^{3,5(10)}$-dienic system in the acid-catalyzed dehydration of the allylic lactone system was obtained by examination of the reaction of 1-keto-$\Delta^{4(10),7}$-santadien-12,5-olide (VI),[5] a product formed from ψ-santonin tosylate. When VI was allowed to react with dilute hydrochloric acid under the usual conditions, a trienic acid displaying an absorption maximum at 240 mμ (ε 10,150) was formed. Such an absorption is characteristic of a heteroannular diene[14] and from a structure such as VI *only the formation of a* $\Delta^{3,5(10)}$*-dienic system* will fit these spectral requirements since a $\Delta^{4(10),5}$-system would give rise to a conjugated triene with the original Δ^{7}-bond and $\Delta^{2,4(10)}$-system would be a homoannular dienone. Accordingly, structure VII must be assigned to the trienic acid. It is of interest to note that the ultraviolet maximum has shifted from 234 mμ in IV to 240 mμ in VII. Such would be expected since it has been shown[16] that a 1,4-dihydrobenzene system in such a position to a chromophore displays a transannular interaction which induces a bathochromic shift. It is of further interest to note that the uniqueness of structure VII lends further support to the position of the double bond in VI, a feature which was employed to establish the stereochemical relationship between the original hydroxyl group and the side chain of ψ-santonin as being *trans*.

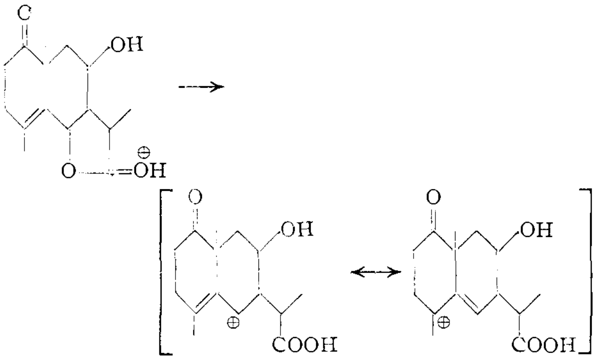


VI



VII

The formation of the $\Delta^{3,5(10)}$-diene structure indicates that the acid-catalyzed elimination is rate controlled for in VII either the establishment of a conjugated triene or a dienone would be thermodynamically favored. Mechanistically, the reaction can be viewed as proceeding by protonization of the lactonic carbonyl group of ψ-santonin and cleavage of the allylic carbon–oxygen bond to give rise to the allylic carbonium ion VIII. Stabilization of the positive charge by hyperconjugation points to structure VIIIb as being of lower energy than VIIIa. The structure of the product will be controlled by the rate of ionization of the hydrogens on the carbon atom adjacent to the carbonium ion.



VIIIa VIIIb

When the santenic acid (IV) is heated to 200°, it is transformed into a lactone which upon alkaline saponification does not regenerate the starting acid. The lactone (as an oil mull) showed absorption in the infrared at 1665 cm.$^{-1}$ (conjugated ketone[12]), 1635 and 1600 cm.$^{-1}$ (conjugated diene[12]) and at 1770 cm.$^{-1}$ (saturated five membered lactone[17]). Furthermore, the lactone displayed an absorption at 320 mμ (ε 5210) also demonstrating that an isomerization of the unsaturated system had occurred.[18] Absorption in this region has been shown to be characteristic for homoannular dienones. For

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(13) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(14) L. F. Fieser, M. Fieser and S. Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948).

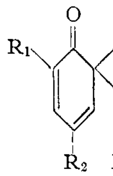
(15) For bibliography of this reaction, see F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930, 5932 (1953).

(16) E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.*, 607 (1949).

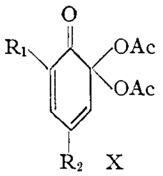
(17) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949), and J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(18) Cocker and Lipman[7] have reported that 1-keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid displayed a weak inflection point at 320 mμ (ε 200) while the material employed in the present work is non-absorbing in this region. The absorption noticed by the former workers would suggest that their acid possessed about 4% of a conjugated homoannular dienone system.

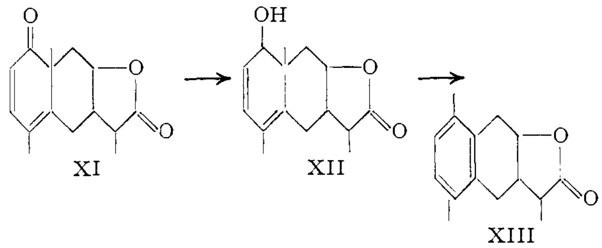
example, Wessely[19] and Cavill[20] have prepared compounds such as IX and X by the action of lead tetraacetate on phenols and the spectra of such compounds containing two alkyl groups on the conjugated system fall in the range 312–318 mμ (ε 4000).[21] Also, it is characteristic of such a system to show an extinction coefficient of the order of 4000. The lactone in the ψ-santonin series which could arise by lactonization of the free hydroxyl with the carboxyl group of IV and concomitant migration of the diene system into conjugation with the carbonyl group and thus possess structure XI, 1-keto-$\Delta^{2,4(10)}$-santadien-12,7-olide, would adequately account for the spectral features observed.[22,23]



IX



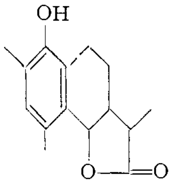
X



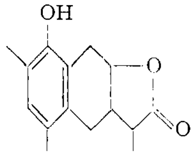
XI XII XIII

The demonstration of the presence of a dienone system by chemical means was attempted by reduction of XI with sodium borohydride to the homoannular dienol (XII). It was found, however, that in order to free the reduction product from the intermediate borate ester acid hydrolysis was required. Such reaction conditions brought about an aromatization of XII and the only product isolated was the lactone XIII. This lactone (in CS_2 solution) showed absorption in the infrared at 1785 cm.$^{-1}$ (saturated five-membered lactone[17]) and at 1875 cm.$^{-1}$ (characteristic of a 1,2,3,4-tetrasubstituted benzene ring[24]). Furthermore, in the ultraviolet, XIII possessed a maximum at 267 mμ (ε 295) which is characteristic of a tetralin structure.[25] Although the demonstration of a homoannular diene was not possible by this method, the formation of the benzenoid lactone devoid of a free oxygen function clearly demonstrates the presence of a readily rearranged dienol system, and for the first time unequivocally establishes the adjacent positions of the carbonyl and angular methyl group. With a compound such as XIII, being free of an oxygen function in the aromatic ring, it should be possible to interrelate ψ-santonin and santonin.

With the establishment of the structure of 1-keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid (IV), the nature of the desmotropo-ψ-santonins can be determined. As discussed earlier, when either ψ-santonin or the santenic acid IV is allowed to react at 50° with 55% sulfuric acid, phenolic lactones are formed and structure XIV has been assigned to



XIV



XV

these desmotropo compounds.[7,9,10] The basic carbon skeleton as well as the position of the phenolic hydroxyl group was established by Cocker[26,27] who showed that when the phenolic lactones were dehydrogenated over palladium, 2,4-dimethyl-6-ethyl-1-naphthol was formed. The position of the lactonic fusion, however, was assigned only on the basis of the earlier, incorrect formula for ψ-santonin. Since acid IV, which is devoid of the hydroxyl at C_5, can be transformed into the desmotropo-ψ-santonins, the position of the lactonic fusion warrants re-examination. It follows, however, that if the phenolic lactones do possess structure XIV, the lactonic hydroxyl group is not that originally present in ψ-santonin but must be formed by lactonization of an unsaturated acid.

It has been shown by infrared spectra that these

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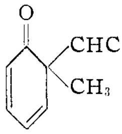
(19) F. Wessely and F. Sinwell, *Monatsh.*, **81**, 1055 (1950), and F. Wessely and J. Koltan, *ibid.*, **84**, 291 (1953).

(20) G. W. K. Cavill, E. R. Cole, P. T. Gilham and D. J. McHugh, *J. Chem. Soc.*, 2785 (1954).

(21) There appears to be an appreciable effect on the maxima (as well as on the displacement of the maximum of the chromophoric system with substitution) of such compounds by the nature of the groups not on the conjugated system. For example, with the unsubstituted compounds (R_1, R_2 = H), IX absorbs at 292 mμ and X at 306 mμ.[19,20] In IX, addition of an alkyl group to the chromophoric system produces a bathochromic shift of 10 mμ while in X, a value of 6 mμ is found. Furthermore, we have examined the compound (b), prepared originally by v. Auwers and Keil (*Ber.*, **35**, 4207 (1902)),



b

and have found that the maximum appears at 299 mμ. Of further interest is the fact that the extinction coefficient of (b) is 19,000, an effect which must be attributed to a strong interaction between the carbonyl and the dichloromethyl groupings.

(22) Recently, a homoannular dienone has been prepared in the ursolic acid series (*Helv. Chim. Acta*, **37**, 2173 (1954)) and its spectral characteristics (λ_{max} 315 mμ, ε 6300) are in excellent agreement with those of the simple models.

(23) The lower extinction coefficient possessed by the homoannular dienones as compared to the heteroannular type would be expected by comparison of the length of the dienone systems in these two types of compounds. In general, "the greater the polarity of the molecule in the ground state, the greater the intensity of the absorption" (F. A. Miller in Gilman's "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 163), and other things being equal, the square of the length of the conjugated system is proportional to the integrated absorption (R. S. Mulliken, *J. Chem. Phys.*, **7**, 364 (1939), R. B. Turner and D. M. Voitle, THIS JOURNAL, **73**, 1403 (1951)). The length of the system (evaluated in a scale drawing and using the values found in L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1945, p. 164) in a heteroannular dienone such as methyl 1,7-diketo-$\Delta^{4(10),5}$-santadienate is 4.5 Å. and in the homoannular dienone XI is 3.6 Å. The ratio of the square of these lengths is 2.25 and the ratio of the integrated absorptions (found by weighing paper patterns of the extrapolated maxima) for these two compounds is 2.18, in excellent agreement with theory.

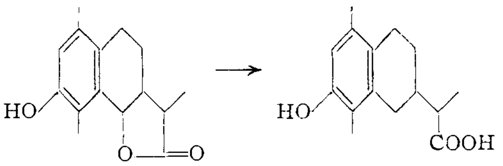
(24) C. W. Young, R. B. DuVall and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

(25) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1951.

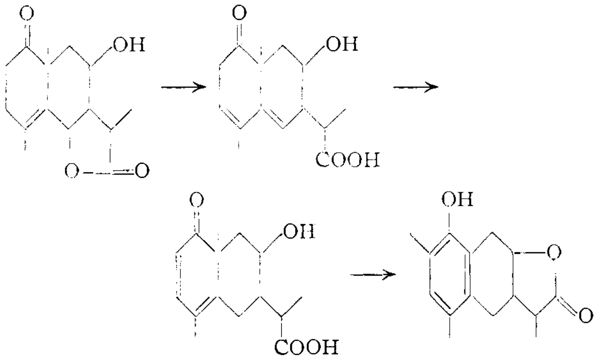
(26) W. Cocker, B. E. Cross, A. K. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson and D. R. A. Whyte, *J. Chem. Soc.*, 1781 (1950).

(27) W. Cocker, A. K. Fateen and C. Lipman, *ibid.*, 929 (1951).

lactones are of the saturated γ-type (1765 cm.$^{-1}$, CHCl$_3$) and upon this basis structure XV would be equally acceptable. A characteristic feature of structure XIV not possessed by XV, however, is the lactonic fusion with a benzylic hydroxyl, a feature also found in the desmotroposantonins (XVI). These latter benzylic lactones display a special re-


XVI XVII

activity in that upon treatment with zinc and acetic acid, they are reduced to desmotroposantonous acids (XVII).[28] It has been found that the desmotropo-ψ-santonins are recovered unchanged from a similar zinc and acetic acid treatment. Such evidence strongly suggests that XV represents the structure of the desmotropo-ψ-santonins and the lactonic hydroxyl in them is that originally present in ψ-santonin at C$_7$. The sequence of acid-catalyzed transformations in this series can be outlined (shown below) as being (1) elimination of the allylic lactone to form a $\Delta^{3,5(10)}$-santadienic acid derivative,



(2) migration of the diene into conjugation to the C$_1$-carbonyl group to form a $\Delta^{2,4(10)}$-santadienic acid and (3) a double Wagner–Meerwein (dienone–phenol) rearrangement with concomitant lactonization to the phenolic lactone.

Experimental[29]

1-Keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic Acid (IV).—Finely powdered ψ-santonin (3.0 g.) and 15 ml. of 6 *N* hydrochloric acid were shaken for 24 hours in a stoppered flask filled with nitrogen. The flask was chilled and the crude product filtered. Recrystallization was conducted so as to avoid excessive heating or contact with oxygen. The crude acid was dissolved in the minimum amount of hot ethanol, and after cooling to room temperature water was added until a turbidity was produced. After crystallization was complete at room temperature, the solution was cooled and the acid filtered. After repetition of this process there was obtained 2.4 g. (80%) of the pure product, m.p. 173.4–174.7°, $[\alpha]^{25}\mathrm{D}$ +63.0° (*c* 0.80, alc.) (lit.[7,8] m.p. 172–173°, $[\alpha]^{16}\mathrm{D}$ +65.4°, for the monohydrate).

Anal. Calcd. for C$_{15}$H$_{20}$O$_4$: C, 68.16; H, 7.63; neut. equiv., 264.3. Found: C, 68.01; H, 7.76; neut. equiv., 266.

The 2,4-dinitrophenylhydrazone was prepared by dissolving 0.20 g. of the acid in 5 ml. of glacial acetic acid and while a stream of nitrogen was passed over the surface of the solution, 0.155 g. of 2,4-dinitrophenylhydrazine was added. The heating was continued for 5 minutes at steam-bath temperature. After cooling and addition of water to turbidity, the product crystallized. The derivative was recrystallized from methanol–water, m.p. 190.0–191.6° (lit.[7] m.p. 193–194°).

Anal. Calcd. for C$_{21}$H$_{26}$O$_8$N$_4$: C, 54.54; H, 5.67; N, 12.12. Found: C, 55.09; H, 5.54; N, 11.87.

1-Keto-$\Delta^{2,4(10)}$-santadien-12,7-olide (XI).—1-Keto-7-hydroxy-$\Delta^{3,5(10)}$-santadienic acid (0.6 g.) was heated, under an atmosphere of nitrogen, for 10 minutes at 200°. After cooling, the glassy residue was triturated with ether in order to induce crystallization. The crystals were filtered, washed with aqueous sodium bicarbonate solution and water and then recrystallized twice from ethanol. The yellow crystalline lactone was obtained in 77% yield (0.5 g.), m.p. 192.8–194.0°, $[\alpha]^{20}\mathrm{D}$ +113° (*c* 1.03, alc.) (lit.[7] m.p. 191–192°, $[\alpha]^{19}\mathrm{D}$ +110°).

α-(1,4-Dimethyl-7-hydroxy-5,6,7,8-tetrahydro-6-naphthyl)-propionic Acid Lactone (XIII).—An aqueous methanolic solution of 2.0 g. of 1-keto-$\Delta^{2,4(10)}$-santadien-12,7-olide and 0.46 g. of sodium borohydride was allowed to stand six days at room temperature and then diluted with 6 *N* hydrochloric acid until an oily phase separated. The mixture was then concentrated under reduced pressure on a steam-bath until a cloudiness appeared. Acetic acid was added to the hot mixture to redissolve the oil and the concentration continued until a semi-crystalline material was deposited. The solid was collected by filtration and recrystallized from benzene–ligroin; yield 0.4 g., m.p. 133–142°. Further recrystallization yielded white needles, m.p. 142–143°. An additional quantity of the material can be obtained by further concentration of the acidified reaction mixture followed by chromatography over alumina.

1-Keto-$\Delta^{3,5(10),7}$-santatrienic Acid (VII).—1-Keto-$\Delta^{4(10),7}$-santadien-12,5-olide[5] (0.1 g.) was powdered and shaken with 6 *N* hydrochloric acid under nitrogen for 24 hours. The crude solid reaction product was recrystallized from aqueous methanol as described for IV, yield 0.9 g., m.p. 130.9–132.0°, $[\alpha]^{25}\mathrm{D}$ +29.6° (*c* 0.30, alc.).

Anal. Calcd. for C$_{15}$H$_{18}$O$_3$: C, 73.15; H, 7.37; neut. equiv., 246. Found: C, 72.75; H, 7.29; neut. equiv., 246.

Treatment of this material with 50% sulfuric acid at 50° gave only a dark, uncharacterizable oil.

(+)-β-Desmotropo-ψ-santonin (XV).[6]—Powdered ψ-santonin (0.50 g.) was stirred into 6 ml. of 50% sulfuric acid and kept at 50° for 20 hours. The reaction mixture was poured into water, extracted with chloroform and the organic phase washed with sodium bicarbonate solution and water. Removal of the solvent and crystallization from alcohol gave 0.27 g. (58%) of the crude phenolic lactone, m.p. 175–180°. Recrystallization from ethanol–water and ethyl acetate–hexane gave pure (+)-β-desmotropo-ψ-santonin, m.p. 186.2–188.5°, $[\alpha]^{25}\mathrm{D}$ +68.7° (*c* 0.95, alc.) (lit.[6] m.p. 185–186°, $[\alpha]^{15}\mathrm{D}$ +68°).

Attempted Zinc-Acetic Acid Reduction of (+)-β-Desmotropo-ψ-santonin.—The lactone (0.20 g.) was refluxed with 0.5 g. of zinc dust and 4 ml. of acetic acid for three hours. The acetic acid was evaporated and the residue dissolved in chloroform. Extraction of the solution with sodium bicarbonate solution yielded no acidic fraction. The remaining neutral material gave 0.17 g. of starting lactone, m.p. 184.3–186.9°.

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(28) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1951, pp. 249–328.

(29) All analyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley. All melting points are corrected.