yield was obtained in a duplicate deamination of the crude diamine.

Anal. Calcd. for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 92.97; H, 6.45.

Synthesis of 7,12-Dihydro-7,12-*o*-benzenobenz[a]anthracene (III).—A mixture of 28 mg. of X and 12 mg. of palladium-on-charcoal was placed in an 8-cm. side-arm test-tube. The tube was flooded with nitrogen and immersed in a salt-bath, the temperature of which was raised from 160 to 300° during 30 minutes. About 5 cc. of gas was collected. The product was dissolved in benzene, filtered and evaporated to dryness. The residue was dissolved in 1 ml. of hexane at 60°. Upon cooling, white plates of III separated. The mother liquor was decanted. The crystals were washed twice with hexane and then dried; weight 23 mg. or 83%, m.p. 208–210°. A mixed melting point with the hydrocarbon prepared from anthracene and 1-nitronaphthalene showed no depression. A mixture of this material with anthracene melted at 170–196°.

A 2,4,7-trinitrofluorenone derivative of the hydrocarbon was prepared, m.p. 185–186°. A mixed melting point with the corresponding derivative of the hydrocarbon obtained from the reaction of anthracene with 1-nitronaphthalene showed no depression. A mixed melting point with the 2,4,7-trinitrofluorenone derivative of anthracene gave a depression of 30°.

Ultraviolet absorption spectra for hydrocarbon III from the two sources were identical. A Beckman quartz spectrophotometer with hydrogen lamp was used. Absorption maxima were noted as follows: ($m\mu$, log ϵ): 245, 4.3; 263–265, 3.6; 272, 3.7; 280, 3.8; 295, 3.6.

7,14-Dihydro-7,14-*o*-benzenobenz[a]naphthacene (XI).—Naphthacene, m.p. 228–230°, was prepared from 1,2,3,4-tetrahydro-6,11-naphthacenequinone heated to 260° in an intimate mixture with zinc dust, sodium chloride and anhydrous zinc chloride by Clar's method.[9]

A mixture of 1.44 g. of naphthacene and 1.5 g. of 1-nitronaphthalene was heated for 10 hours at 275° in an open flask. Nitric oxide was evolved, and the reaction product was a black, pitch-like material partially soluble in benzene. Passage of the benzene solution over a column of alumina yielded 0.28 g. of white substance, which when recrystallized from hexane melted at 214–215°.

Anal. Calcd. for $C_{28}H_{18}$: C, 94.88; H, 5.12. Found: C, 95.08; H, 5.16.

A 2,4,7-trinitrofluorenone addition compound of XI was prepared in 80% yield by adding 5 ml. of a hot saturated solution of 2,4,7-trinitrofluorenone in alcohol to a solution of 0.1 g. of the hydrocarbon in 5 ml. of benzene. A portion was recrystallized from alcohol and melted 191–192.5°.

Anal. Calcd. for $C_{24}H_{28}N_6O_{14}$: C, 65.85; H, 2.86. Found: C, 65.85; H, 3.09.

2-Methyl-5,5a,6,11,11a,12-hexahydro-5,12-*o*-benzenonaphthacene.—2-Methylanthracene, m.p. 205–207°, was prepared by prolonged hot alkaline zinc dust reduction of 2-methylanthraquinone (in toluene) by adapting Martin's directions[10] for anthraquinone. The yield was 25%.

A mixture of 2.6 g. of 85% 1,4-dihydronaphthalene and 2.7 g. of 2-methylanthracene was sealed into a glass tube and heated for 12 hours at 245°. After opening the tube, the product was removed with the aid of benzene. Evaporation of the benzene solution left a residue which was fractionally crystallized from ligroin (b.p. 60–71°) and alcohol to give 0.75 g. (16.7%) of a white crystalline compound, m.p. 165–167°.

Anal. Calcd. for $C_{25}H_{22}$: C, 93.14; H, 6.88. Found: C, 92.91; H, 6.71.

2-Methyl-5,12-dihydro-5,12-*o*-benzenonaphthacene (XII).—Dehydrogenation of the above hydrocarbon was accomplished by heating 0.25 g. of it with palladium-on-charcoal for an hour to a maximum temperature of 255°. Hydrogen (30 cc.) was evolved. The product was recrystallized from absolute alcohol to give 0.2 g. (81%) of a white crystalline compound (XII), m.p. 174–176°. A mixed melting point determination with the starting material was 140–165°.

Anal. Calcd. for $C_{25}H_{18}$: C, 94.32; H, 5.70. Found: C, 94.05; H, 5.73.

Acknowledgment.—We are grateful to Great Lakes Carbon Corporation for generous financial support to one of us (L. J.) during the period of this work.

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[9] E. Clar, *Ber.*, **72**, 1645 (1939).

[10] E. L. Martin, THIS JOURNAL, **58**, 1438 (1936).

EVANSTON, ILLINOIS

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

The Structure of ψ-Santonin

BY WILLIAM G. DAUBEN AND PAUL D. HANCE[1]

RECEIVED AUGUST 20, 1954

The relative positions of the hydroxyl group, the lactone and the olefinic double bond in ψ-santonin have been determined. It was found that both the free hydroxyl group and the lactonic hydroxyl group are gamma to the carboxyl group of the side-chain and that the hydroxyl grouping is secondary. The carbon–carbon double bond was shown to be tetrasubstituted and in the ring opposite but allylic to the lactonic hydroxyl group. It was demonstrated that in the dihydrogenation of ψ-santonin, hydrogenolysis of the lactone ring occurred. A new structure for this sesquiterpene has been postulated and preliminary results with regard to the stereochemistry of the molecule have been discussed.

ψ-Santonin is one of the sesquiterpenic lactones isolated from various species of the plant family Artemisia[2] and the structure of this compound has received considerable attention.[3,4] Degradation studies by Clemo and Cocker[5] and Cocker and his co-workers[3] have established that ψ-santonin has a normal isoprenoid structure of the eudalene group, a carbon skeleton also possessed by santonin, β-santonin and artemisin which occur in the same plant family.[6] In addition to the lactonic function, the presence of a carbonyl group, a free hydroxyl and a carbon–carbon double bond also have been demonstrated, but of the latter groupings only the carbonyl group has been established fairly firmly as being located at C_1.[7] Recently, Dauben and Hance[4] reported an extensive study with

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

[2] Messrs. T. and H. Smith, Ltd., *Pharm. J.*, **80**, 3 (1935).

[3] W. Cocker, B. E. Cross and D. H. Hayes, *Chemistry & Industry*, 314 (1952), and earlier papers.

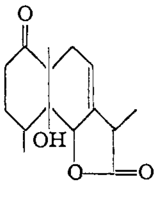
[4] W. G. Dauben and P. D. Hance, THIS JOURNAL, **75**, 3352 (1953).

[5] G. R. Clemo and W. Cocker, *J. Chem. Soc.*, 30 (1946).

[6] An excellent summary of these structural studies is to be found in J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, University Press, Cambridge, England, 1951.

[7] The ring numbering system employed in the present paper differs from that suggested by Cocker[3] in that the reactive carbonyl group is called C_1 rather than C_4. For details of the present numbering system as well as changes in nomenclature see footnote 10.

regard to the position of the double bond in relationship to the lactone ring and it was found that these two functional groups were not of the α,β- or β,γ-unsaturated lactone type. It was concluded that the double bond was at least two carbon atoms removed from the lactonic carbonyl group, and on the basis of the then existing structural formulation for ψ-santonin, a β,γ'-type of unsaturated lactone I was favored. Such placement of the double bond was indicated by the ready hydrogenolysis of the lactone ring and the exact location rested upon the presence of a tertiary hydroxyl group at the other allylic position. In view of the importance of this latter assumption by Clemo and Cocker,[5] the location of the hydroxyl group was studied further.



I

The original assignment of the hydroxyl group of ψ-santonin as tertiary function placed at C_{10} was made by Clemo and Cocker[5] on the basis of the fact that the compound was acetylated with difficulty and in low yield (30%). The crystalline product so obtained, however, upon saponification yielded a material isomeric with ψ-santonin. It was ascertained that the alkaline conditions employed for the saponification did not bring about any changes in ψ-santonin itself. Accordingly, it was suggested that the acetate was derived from a product of molecular rearrangement which could have occurred during the acetylation.

Reinvestigation of the reactivity of the hydroxyl group showed, however, that ψ-santonin reacts readily with acetic anhydride and sodium acetate under the conditions of Clemo and Cocker[5] to yield a liquid acetate II in 70% yield. All attempts to crystallize the material have failed but the acetate upon saponification yielded starting ψ-santonin.

In addition to the liquid acetate, ψ-santonin yields crystalline cathylate (ethyl carbonate) III and tosylate IV esters in 80 and 86% yield, respectively. Fieser[8] has shown that in the steroid series ethyl chlorocarbonate is a more sterically selective reagent than acetic anhydride. This knowledge, when coupled with the fact that no tosylate esters of tertiary alcohols are known to exist,[9] is strongly suggestive that the alcoholic function of ψ-santonin is not tertiary. Furthermore, the difficulty of dehydrating the sesquiterpenic lactone under non-rearrangement conditions agrees with this conclusion. Although attempts to eliminate the elements of water either by treatment with phosphorus pentoxide or phosphorus oxychloride and pyridine yielded only oils which could not be obtained crystalline, when the tosylate IV was heated at 150° for three days with 2,4,6-collidine, a crystalline anhydro-ψ-santonin V could be isolated in good yield.

Additional evidence as to the nature of this hydroxyl grouping was gained by oxidation of ψ-santonin with chromic acid in acetic acid. A product was isolated in 70% yield which possessed the proper analytical values for a diketone, $C_{15}H_{18}O_4$, but the material melted with a broad and variable range. The intensity of the carbonyl band both in the ultraviolet and the infrared was double that of the starting material. The presence of a single carbonyl band at 1713 cm.$^{-1}$ further suggested that both carbonyl functions belong to a six-membered ring and that the original hydroxyl grouping is secondary.

The reactions of 1-keto-7-hydroxysantenic acid[10] (dihydro-ψ-santonin) also are of importance when considering the nature of the free hydroxyl group. This acid VI, the hydrogenolysis product of ψ-santonin, must possess the original hydroxyl grouping and be formed by hydrogenolysis of the lactone ring since it has been found that hydrogenation of ψ-santonin acetate (II) yielded 1-keto-7-acetoxysantenic acid. Saponification of the acetate gave the free acid VI. When VI was boiled with 98% formic acid, instead of dehydration occurring as would be expected of a tertiary alcohol, a good yield of the formate ester of VI was obtained. That no rearrangement of the molecule had occurred was shown by ready saponification of the ester to the starting acid VI. To further establish that actual esterification had occurred and not formation of a mixed anhydride, the methyl ester of the formate was prepared with diazomethane. Furthermore, simple addition of formic acid to the double bond[11] was ruled out on the basis of elementary analysis. In line with this stability of the hydroxyl function is the fact that 1-keto-7-hydroxysantenic acid is stable to 50% sulfuric acid, conditions which readily convert ψ-santonin to the phenolic desmotropo-ψ-santonin.

The results of the Kuhn–Roth oxidation on the compounds in this series also are of aid in characterizing the nature and location of the hydroxyl grouping. If it be accepted that ψ-santonin possesses the eudalene carbon skeleton, then there are three potential C-methyl groups as determined by this oxidation method. The presence of a primary

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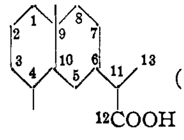
[8] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero and T. Utne, THIS JOURNAL, **74**, 3309 (1952); L. F. Fieser and G. Ourisson, *ibid.*, **75**, 4404 (1953).

[9] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 514.

[10] Clemo and Cocker,[5] in their original work, gave many trivial names to reaction products before the structures were determined. For example, the hydrogenation product ($C_{15}H_{22}O_4$) of ψ-santonin ($C_{15}H_{20}O_4$) was called dihydro-ψ-santonin. Since it has been shown that the reaction product actually is an acid resulting from hydrogenolysis of the lactone ring, it is desirable that this material be renamed in a manner to indicate the change. It has been suggested by Professor D. H. R. Barton that since all compounds related to santonin, β-santonin, artemisin and ψ-santonin possess the same carbon skeleton, they all be named as derivatives of the hypothetical nucleus *Santanic acid* (a). Accordingly, dihydro-ψ-santonin would become 1-keto-7-hydroxysantenic acid. The position of the double bond is not given since its position is not known with certainty.



(a)

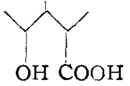
[11] H. B. Knight, R. E. Koos and D. Swern, THIS JOURNAL, **75**, 6212 (1953).

hydroxyl grouping on any of these C-methyl groups should lower the number of potential C-methyl groups. On the other hand, a secondary hydroxyl group only can be located on the ring system and as such should not affect the yield of acetic acid. It has been found that ψ-santonin as well as all of its derivatives yield between 2.0–2.6 moles of acetic acid per mole of compound or values expected for a compound with three C-methyl groups. Thus, all evidence suggests a nuclear secondary hydroxyl grouping.

The exact location of this hydroxyl function has been determined by a study of the lactones in the ψ-santonin series as well as by oxidation and elimination reactions. It has been well established that the frequency at which a lactonic carbonyl grouping absorbs in the infrared is dependent upon the size of the lactone ring, a γ-lactone absorbing at 1770 cm.$^{-1}$ and a δ-lactone at 1740 cm.$^{-1}$.[12]

Two lactones are of particular interest in this present study. As has been discussed earlier, in the hydrogenolysis of ψ-santonin to 1-keto-7-hydroxy-santenic acid (VI), the original hydroxyl of the sesquiterpenic lactone remains. When VI is heated with acetic anhydride, the lactone of VI, 1-keto-santen-12,7-olide (VII), is obtained. Also, further reduction of VI first with sodium amalgam and then with platinum and hydrogen in acetic acid yields 1,7-dihydroxysantanic acid (VIII). This saturated dihydroxy acid on treatment with acetic anhydride gives rise to the acetate lactone of VIII, 1-acetoxy-santan-12,7-olide (IX). In both of these cases, lactonization occurs on the original hydroxyl group of ψ-santonin. It has been found that lactones VII and IX display lactonic carbonyl bands at 1769 and 1763 cm.$^{-1}$ ($CHCl_3$), respectively, thus indicating the presence of a γ-lactone in each case. It might be pointed out that if the hydroxyl group were of the tertiary type suggested by Clemo and Cocker,[5] then a δ-lactone would have been obtained and hence the above infrared results give further substantiation to the non-tertiary nature of the alcoholic function.

The nature of the original lactone in ψ-santonin has been discussed by Dauben and Hance[4] and on the basis of a lactone carbonyl band at 1762 cm.$^{-1}$ (CH_2Cl_2) they suggested that it could be a saturated γ-lactone. It now has been found that the lactone band in the acetate and the cathylate of ψ-santonin is at 1775 and 1773 cm.$^{-1}$ (CCl_4), respectively, thus clearly indicating the presence of a saturated γ-lactone. Hence, both lactonic hydroxyl and the free hydroxyl grouping in ψ-santonin are in a γ-position relative to the α-propionic acid side-chain. Accordingly, the two hydroxyl functions must be arranged as shown in the partial structure X. On the basis of earlier work,[4] it was concluded that the olefinic center was of the allylic type, shown in partial structure XI, but in view of the new placement of the free hydroxyl group such a formulation must be discarded. An alternate allylic arrangement, as XII does fit the chemical and spectral data for ψ-santonin and combination of all of these facts (a) two γ-hydroxyl groupings, (b) an allylic lactone and (c) a eudalene structure, permits only one structure (XIII) to be assigned to ψ-santonin and that places the hydroxy group at C_7 and the double bond between C_5 and C_{10}. If the double bond of ψ-santonin is assumed not to migrate during the hydrogenolysis of the lactone ring, it follows that structure VI represents 1-keto-7-hydroxysantenic acid and VIII represents 1,7-dihydroxysantanic acid. The lactones of these latter two compounds (VII and IX) then would be fused at C_7.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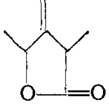
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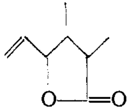
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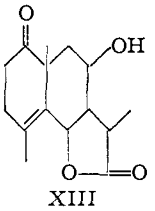
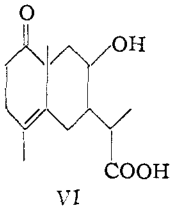
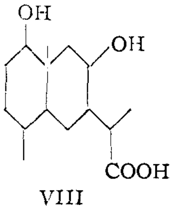

XIII


VI


VIII

This new formulation places the unsaturation of ψ-santonin as a tetrasubstituted double bond and evidence for this structural feature is to be found by examination of the ultraviolet spectrum of the lactone. As has been reported earlier,[4] the spectrum of ψ-santonin displays no high intensity maximum in the 205–250 mμ region, but it does show intense absorption between 205–220 mμ; the values of the extinction coefficients at 210, 215 and 220 mμ are 8300, 6000 and 3500, respectively. It has been shown by Bladon, Henbest and Wood[13] that such an absorption pattern is characteristic of a tetrasubstituted olefinic double bond. Furthermore, it was demonstrated that the foregoing absorption was due to the double bond, for when ψ-santonin was allowed to react with performic acid a crystalline epoxide[5] was obtained; the extinction coefficients of this material at 210, 215 and 220 mμ are 170, 140 and 100, respectively. The previous examination[4] of the carbon–hydrogen stretching frequency in the 3000 cm.$^{-1}$ must be assumed to have been incorrectly assigned and further work is called for in this regard.

The placement of the hydroxyl function at C_7 throws new light upon the nature of the product received by the chromic acid oxidation of ψ-santonin. As has been reported above, an analytically pure compound possessing a wide melting range could be obtained. Examination of the structure of such a product (XIV) shows that the lactonic hydroxyl not only is of the allylic type but also is β to a carbonyl group. The elimination of such a hydroxyl function should be facile and catalyzed by either acid or base. It has been found that when the crude oxidation product was saponified with dilute alkali an oily acid was obtained along with a small quantity of ψ-santonin. The crude acid was esterified with diazomethane and the

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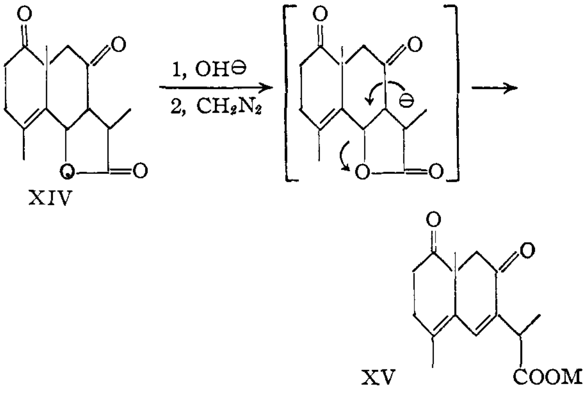
[12] R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

[13] P. Bladon, H. B. Henbest and G. W. Woods, *J. Chem. Soc.*, 2737 (1952).

resulting yellow oil solidified on standing. This solid material possessed an analysis calculated for the ester of the elimination product XV, $C_{16}H_{20}O_4$,

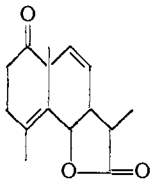


XIV

XV

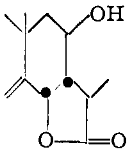
and the ultraviolet spectrum of the ester showed an intense maximum at 307 mμ (ε 12,270), values which are in good agreement with the calculated value of 314 mμ for a heteroannular dienone. Furthermore, it was found that when the crude oxidation product was allowed to react with semicarbazide hydrochloride in pyridine, a disemicarbazone was obtained which was soluble in sodium bicarbonate and which displayed absorption bands of high intensity at 227 mμ (ε 16,080) and 305 mμ (ε 29,000). Such values are to be expected of the semicarbazone of the isolated ketone and the conjugated dienone system present in XV.[14] Thus, compound XV clearly related the relative positions of the double bond, the lactonic hydroxyl and the free hydroxyl of ψ-santonin and corroborates the postulated formulation XIII.

An indication of the stereochemistry of ψ-santonin can be gained by examination of the structure of anhydro-ψ-santonin (V) which was obtained by elimination of *p*-toluenesulfonic acid from ψ-santonin tosylate. There are two possible positions for the new double bond, C_6–C_7 or C_7–C_8. In the former a trisubstituted linkage would be introduced and in the latter a disubstituted. Since it is characteristic of a trisubstituted olefinic linkage to increase the intensity of the spectrum in the 205–220 mμ region by about 3000 while a disubstituted bond produces practically no effect,[13] and since the spectrum of the anhydro product is practically identical with that of ψ-santonin, a C_7–C_8 structure has been assigned to V. Furthermore, if elimination had occurred to give a double bond at C_6–C_7, the compound would be a β,γ-unsaturated lactone and such a structure in the presence of collidine *p*-toluenesulfonate at 150° would be expected to equilibrate with its α,β-isomer.[15] This latter isomer should show absorption near 220 mμ and such was not found. In the infrared, the only difference noted between the anhydro compound V and the starting hydroxy lactone XIII is the disappearance of the hydroxyl band and the appearance of a new band at 3050 cm.$^{-1}$, a band which is characteristic of an olefinic C–H stretch.



V

It is well established that the base-catalyzed elimination of a tosyl group is a *trans* elimination and that when such stereochemical requirements are met by elimination toward a methine as well as a methylene group, the reaction toward the methine grouping is favored.[16] Since with ψ-santonin tosylate, the direction of elimination appears to be away from the methine grouping, it can be assumed that the hydroxyl group and the tertiary hydrogen on C_6 are *cis*, thus making the hydroxyl *trans* to the propionic acid side-chain. Further proof of this stereochemical arrangement has been sought by the investigation of the pyrolysis of the acetate and the cathylate, a reaction which should proceed by a *cis* elimination.[17] To date, no pure materials have been obtained from such reactions and the study is being continued. With regard to the stereochemistry of the original lactone in ψ-santonin, it is to be noted that not only is relactonization facile as compared to that observed in other compounds in this series, but also that upon such relactonization only the starting material is obtained. This greater reactivity of the original γ-lactonic hydroxyl toward ring closure cannot be due to its allylic nature for, in general, such unsaturated alcohols esterify about half as fast as the saturated alcohols.[18] It is possible that such ease of lactonization may be due to the formation of a *cis*-lactone as compared to a *trans*-lactone formation if reaction occurs on the C_7-hydroxyl group. Accordingly, a partial formula can be postulated



Acknowledgment.—The authors wish to thank Messrs. T. and H. Smith, Ltd., Edinburgh, Scotland, for kindly supplying the ψ-santonin used in this work.

Experimental[19]

ψ-Santonin Acetate (II).—ψ-Santonin (0.5 g.) was refluxed for one hour with 2 ml. of acetic anhydride and 0.5 g. of anhydrous sodium acetate. The excess acetic anhydride was removed under reduced pressure and the residue dissolved in ether, the ethereal solution washed with aqueous sodium carbonate solution, water and then dried. After

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[14] L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

[15] J. Cason, N. L. Allinger and D. E. Williams, *J. Org. Chem.*, **18**, 842 (1953).

[16] C. K. Ingold, "Structure and Reactivity in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 468–472.

[17] D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949); E. R. Alexander and E. Mudrak, THIS JOURNAL, **72**, 1810 (1950); G. L. O'Connor and H. R. Nace, *ibid.*, **74**, 5454 (1952).

[18] A. Kailan and S. Schwebel, *Monatsh.*, **63**, 52 (1953).

[19] All analyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley. All melting points are corrected. The infrared spectra were obtained with a model 21 Perkin–Elmer spectrophotometer using sodium chloride optics and the cells were approximately 0.1 mm. thick. The solvent employed is given after each value.

removal of the solvent, the acetate was distilled in a short-path molecular still with a bath temperature of 120° and a pressure of 0.3 mm. The yield of a clear sticky glass was 0.5 g. (69%), $[\alpha]^{25}\text{D}$ −137.7° (*c* 0.49, alc.).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.64; H, 7.24. Found: C, 66.85; H, 7.45.

Chromatography of this material yielded no solid material. The solid acetate reported by Clemo and Cocker[5] melted at 187°, $[\alpha]^{20}\text{D}$ −69.2°.

ψ-Santonin Cathylate (III).—To a solution of 0.5 g. of ψ-santonin in 3 ml. of dry pyridine and 3 ml. of dry benzene at 0° was added 0.7 ml. of ethyl chlorocarbonate in 2 ml. of dry benzene. After standing at room temperature for 2 hours, the reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and water and then dried. After filtration through a short column of alumina and removal of the solvent, the residue was recrystallized from ether–hexane; yield 0.5 g. (79%), m.p. 171.9–174.3°. Sublimation followed by recrystallization yielded material melting from 174.3–175.8°, $[\alpha]^{25}\text{D}$ −108.5° (*c* 0.37, alc.).

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.12. Found: C, 64.40; H, 7.01.

ψ-Santonin Tosylate (IV).—ψ-Santonin (1.0 g.) was dissolved in 4 ml. of dry pyridine and 0.75 g. of *p*-toluenesulfonyl chloride was added. After warming at 50–60° for 12 hours, the cooled reaction mixture was poured into water and extracted with benzene. The benzene solution was washed with dilute hydrochloric acid and aqueous sodium bicarbonate solution, dried and filtered through a short column of alumina. After concentration of the eluate and addition of hexane, 1.37 g. (86%) of the tosylate was obtained, m.p. 132.8–135.0°, $[\alpha]^{25}\text{D}$ −110.0° (*c* 0.54, alc.).

Anal. Calcd. for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.66. Found: C, 63.46; H, 6.51; S, 7.55.

Anhydro-ψ-santonin (V).—ψ-Santonin tosylate (0.9 g.) was heated with 10 ml. of 2,4,6-collidine and 5 ml. of toluene in an oil-bath at 150° (temperature must be kept below 155° to avoid extensive decomposition) for 3 days. The cooled reaction mixture was poured into water, extracted with benzene and the extract washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and dried. The solution was concentrated and the product crystallized twice from benzene–hexane; yield 0.36 g. (68%), m.p. 128.2–130.3°, $[\alpha]^{25}\text{D}$ −240.0° (*c* 0.51, alc.). The ultraviolet spectrum is essentially identical with that of ψ-santonin.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.94; H, 7.60.

Hydrogenolysis of ψ-Santonin Acetate.—Crude ψ-santonin acetate (0.25 g., undistilled) was hydrogenated over palladium-on-charcoal in acetic acid at 45 lb. for 40 minutes. After filtration of the catalyst and evaporation of the solvent, the residue was crystallized twice from methanol–water to yield 0.180 g. of 1-keto-7-acetoxysantenic acid, m.p. 136.8–138.0°. The product was soluble in aqueous sodium bicarbonate solution. Saponification of the material yielded 1-keto-7-hydroxysantenic acid, m.p. 188–190°, which did not depress the melting point of an authentic sample.

1-Keto-7-hydroxysantenic Acid Formate.—1-Keto-7-hydroxysantenic acid (0.5 g., m.p. 191.0–193.4°, $[\alpha]^{25}\text{D}$ −3.3° (*c* 1.01, alc.), −6.6° (*c* 0.635, HOAc))[20] was refluxed with 3 ml. of 98% formic acid for 3 hours. The excess formic acid was evaporated under a stream of dry air and the residue was dissolved in ether, washed with water, dried and the product recrystallized from ether–hexane. The crude formate (0.41 g., 74%) had a melting point of 134–138°. Sublimation and recrystallization yielded an ester of melting point 141.8–143.4°.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.54; neut. equiv., 294; sapn. equiv., 147. Found: C, 65.34; H, 7.50; neut. equiv., 276; sapn. equiv., 149.

A sample was saponified and yielded 1-keto-7-hydroxysantenic acid, m.p. 187.3–191.0°.

The formate ester was esterified with diazomethane and the product recrystallized from ether–hexane; m.p. 108.0–109.8°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.02; H, 7.67.

1-Keto-santen-12,7-olide (VII).—The hydroxy acid (1.0 g.) was refluxed for 2 hours with 5 ml. of acetic anhydride and a drop of pyridine. The excess acetic anhydride was removed under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, dried and the solvent removed. The residue (0.7 g.) melts from 150–158°. The crude lactone was chromatographed on alumina, the lactone being removed with benzene. Recrystallization of the product from methanol yields lactone of m.p. 155.7–158.0°, $[\alpha]^{25}\text{D}$ −138.9° (*c* 0.81, alc.) (lit.[5] m.p. 158°).

1-Acetoxy-santan-12,7-olide (VIII).—This compound was prepared according to the method of Clemo and Cocker.[5] Recrystallization of the product twice from ether–hexane yielded the lactone acetate, m.p. 125.8–127.5° (lit.[5] 125°), $[\alpha]^{25}\text{D}$ −54.0° (*c* 0.57, alc.).

1,7-Diketo-$\Delta^{4(10)}$-santen-12,5-olide (XIV).—To 3 ml. of a 3 *N* chromic acid–acetic acid solution was added 1.0 g. of ψ-santonin dissolved in 80% acetic acid. The solution was allowed to stand at room temperature for 2 hours and then overnight at 5°. The reaction mixture was poured into water, extracted with chloroform and the extract washed with aqueous sodium bicarbonate solution and dried. Removal of the solvent and crystallization of the residue from ether–hexane gave 0.7 g. of crystals, m.p. 121–125°, which upon recrystallization yielded crude dione XIV, m.p. 132–137°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.86; H, 7.23.

Further fractional crystallization of the compound from benzene yielded impure ψ-santonin and dione of m.p. 139.2–146.0°. When the material, prior to benzene crystallization, was sublimed and recrystallized, the product melts from 150–180°. Chromatography on alumina yielded about 10% of impure ψ-santonin, m.p. 178–183°, while the remainder of the material formed a stationary pink band at the top of the column.

When the crude dione (0.30 g., m.p. 139–146°) was treated with 2.5 equiv. of semicarbazide hydrochloride in a mixture of pyridine and ethanol and heated on the steam-bath for 2 hours, evaporation of the solvent and dilution with water yielded a light yellow solid. The material could not be recrystallized, but was precipitated from methanol by the addition of water or ethyl acetate; yield 0.10 g., m.p. 205–207°. The yellow solid was soluble in sodium bicarbonate, thus suggesting that it is the disemicarbazone of the diene-dione acid.

Anal. Calcd. for $C_{17}H_{24}O_4N_6$: C, 54.24; H, 6.43; N, 22.33; neut. equiv., 376. Found: C, 52.94; H, 6.53; N, 20.30; neut. equiv., 404.

Methyl 1,7-Diketo-$\Delta^{4(10),6}$-santadienate (XV).—The crude product (0.25 g.) from the chromic acid oxidation of ψ-santonin was saponified with 0.5 *N* sodium hydroxide by allowing it to stand overnight at room temperature under nitrogen. The dark red solution was acidified, extracted with chloroform and the extract washed with water and dried. The solvent was removed under reduced pressure and the residue esterified with diazomethane. After removal of the solvent, the material was dissolved in ether, a small volume of hexane added and, upon standing, 0.03 g. (12%) of ψ-santonin crystallized. The filtrate was concentrated and the residue distilled through a short-path molecular still to yield 0.17 g. of a yellow oil which slowly solidified on standing; m.p. 40–53°, $[\alpha]^{25}\text{D}$ +189.9° (*c* 0.39, alc.). The solid could not be recrystallized.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.33; H, 7.48.

ψ-Santonin Epoxide.—The compound was prepared following the general method of Clemo and Cocker[5] except that performic acid was used in place of perbenzoic acid. The material melts from 139.4–143.4° (lit.[5] 145.5–146.5°).

Kuhn–Roth C-Methyl Determinations.—The procedure employed was that described by Pregl and Grant[21] and the results, given in moles of acetic acid per mole of compound, are as follows: ψ-santonin, 2.60; 1-keto-7-hydroxysantenic acid, 2.35; 1,7-dihydroxysantenic acid, 2.38; 1,7-dihydroxysantanic acid, 2.05; ψ-santonic acid lactone, 2.21; desmotropo-ψ-santonin, 2.30.

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[20] Clemo and Cocker[5] report a value of $[\alpha]^{20}\text{D}$ −239 (*c* 0.96, HOAc) for this material. We have never obtained a compound with this rotation. The former authors report a m.p. of 188–189°.

[21] F. Pregl and J. Grant, "Quantitative Organic Microanalysis," The Blakiston Co., Philadelphia, Penna., 1946, p. 167.