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The Stereochemistry of ψ-Santonin[1]

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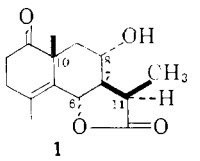
Previous studies pertaining to the stereochemistry of ψ-santonin are discussed. In the present work, further evidence for the *trans* relationship between the C-7 side-chain and the C-8 hydroxyl group was found by the preparation of 8-epi-ψ-santonin (10) and a study of its reactions. The *cis* nature of the 6,12-lactone was established: (a) by evaluation of the steric demands of the reactions employed to resynthesize ψ-santonin from 4, (b) by evaluation of the steric requirements needed for hydrogenolysis of an allylic lactone, and (c) by establishment of the structure of iso-ψ-santonin as an 11-iso derivative (14). The stereochemistry of the C-11 methyl group was shown to be the same as in (−)-α-santonin by a study of the stability of the isomeric desmotropo-ψ-santonins. Further, it was found that (+)-α-isodesmotropo-ψ-santonin possessed structure **35a** rather than **32** previously assigned. The stereochemistry of ψ-santonin is represented by **43**.

ψ-Santonin is a sesquiterpene lactone isolated from *Artemisia* and on the basis of a series of chemical transformations was assigned the gross structure **1**.[3-6] By consideration of the steric demands of certain of the transformations, Cocker and his coworkers[7] suggested the steric representation shown in **1**.[8] During the course of our continuing investigation of the chemistry of the interesting material,



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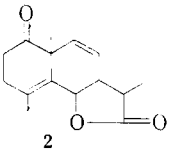
results have been obtained which permit an unequivocal assignment of configuration to all of the asymmetric centers and necessitate a minor revision of formula **1**. The importance of the stereochemistry of this material stems from the fact that it has served as a relay in relating the sesquiterpenic lactones (−)-α-santonin and artemisin[9] to alantolactone[10,11] and costol[12,13] which, in turn, have been related to β-selinene[14,15] whose absolute configuration is known. As a result of these transformations, the absolute stereochemistry of the side-chain at C-7 and the angular methyl group at C-10 of ψ-santonin is known with certainty.

The configuration of the C-8 hydroxyl group as *trans* to the C-7 side-chain can be assigned on the basis of various results. First, the dehydration of ψ-santonin is difficult, suggesting an equatorial conformation and hence a *trans* relationship to the C-7 side-chain which is equatorial. Also, this dehydration does not involve the usually preferred tertiary hydrogen on C-7, but a 8,9-ene (**2**) is formed.[3] Second, the lactone **3**, derivable from ψ-santonin,[10] is identical with a tetrahydroalantolacetone isomer which is known to possess a *trans*-lactone grouping.[11] Third, by application of the lactone rule of



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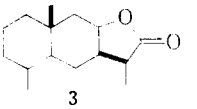

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Klyne[16] concerning the absolute configuration of the potential hydroxyl group it can be concluded[17] that the oxygen function possesses an opposite absolute configuration to that of C-7 side-chain and C-10 methyl group. Further evidence of the *trans* relationship now has been obtained. It has been reported previously[4] when ψ-santonin (**1**) is hydrogenated that hydrogenolysis of the allylic lactone with concomitant migration of the double bond occurs to yield the hydroxy acid **4**. This acid shows no tendency to lactonize spontaneously, and to obtain the lactone **5** it must be treated with acetic anhydride. When the tosylate of ψ-santonin (**6**) was hydrogenated under similar conditions, one

(1) For the previous paper in this series, see THIS JOURNAL, **80**, 5704 (1958).

(2) Du Pont Teaching Fellow, 1956–1957.

(3) W. G. Dauben and P. D. Hance, THIS JOURNAL, **77**, 606 (1955).

(4) W. G. Dauben and P. D. Hance, *ibid.*, **77**, 2451 (1955).

(5) W. G. Dauben, P. D. Hance and W. K. Hayes, *ibid.*, **77**, 4609 (1955).

(6) N. W. Chopra, W. Cocker, B. E. Cross, J. T. Edward, D. H. Hayes and H. P. Hutchinson, *J. Chem. Soc.*, 588 (1955).

(7) N. W. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry and E. R. Stuart, *ibid.*, 1828 (1956).

(8) In this present work, the previously defined santanic acid nomenclature[3] is used but has been modified so that the numbering of the positions resembles that of a steroidal system rather than a decalin system.

(9) M. Sumi, W. G. Dauben and W. K. Hayes, THIS JOURNAL, **80**, 5704 (1958).

(10) W. Cocker and T. B. H. McMurry, *Proc. Chem. Soc.*, 147 (1958); *J. Chem. Soc.*, 1998 (1959).

(11) K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, THIS JOURNAL, **79**, 5721 (1957).

(12) T. Ukida and S. Nakazawa, *Pharm. Bull., Tokyo*, **2**, 239 (1954).

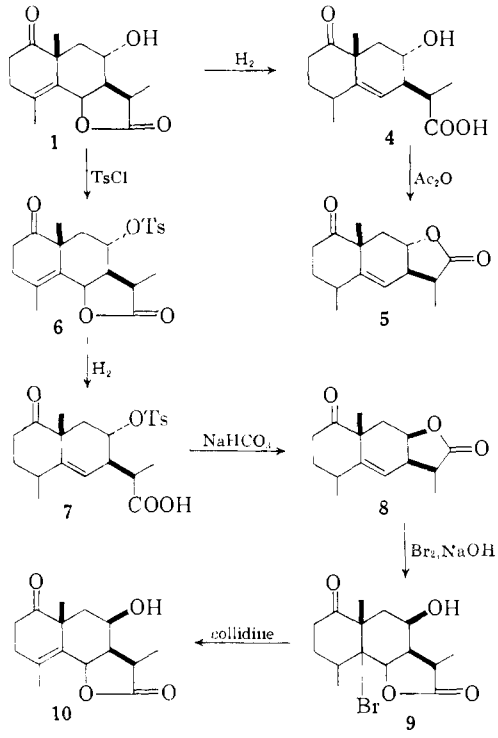
(13) V. Benesova, V. Sykora, V. Herout and F. Sorm, *Chemistry & Industry*, 363 (1958).

(14) K. Tanabe, *Pharm. Bull., Tokyo*, **5**, 623 (1957).

(15) B. Riniker, J. Kalvoda, D. Arigoni, A. Furst, O. Jeger, A. M. Gold and R. B. Woodward, THIS JOURNAL, **76**, 313 (1954).

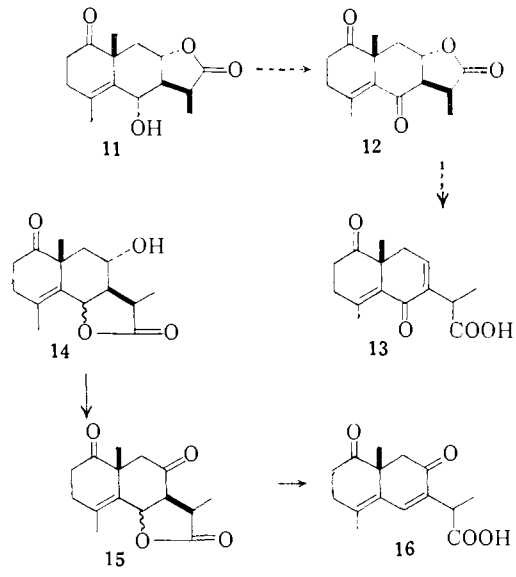
(16) W. Klyne, *Chemistry & Industry*, 1198 (1954).

(17) N. M. Chopra, W. Cocker and J. T. Edwards, *ibid.*, 1535 (1954).



mole of hydrogen was absorbed rapidly and the resulting product **7** was not isolated but treated directly with sodium bicarbonate. From this reaction sequence the lactone **8** was isolated and the 8-*epi* configuration was assigned since inversion would be expected in the displacement of the tosylate grouping by the carboxylate anion. The lactone upon saponification and then acidification was recovered and the spontaneous lactonization indicated a *cis* relationship in the lactone. That, indeed, lactone **8** differed from **5** only by the configuration of the C-8 hydroxyl function was shown by its reaction in basic solution with bromine to form the bromo-lactone **9**. This latter material upon dehydrobromination yielded the lactone **10**, 8-epi-ψ-santonin, which possessed spectral properties identical with those of ψ-santonin. It has previously been shown that this same reaction sequence transforms **4** to ψ-santonin and, hence, the similarity of the reaction sequence indicates correctness of the above assignment of structures. The lactonic carbonyl absorption in the infrared further substantiated the epimeric difference in that the band was at 1770 cm.$^{-1}$ in **5** and at 1755 cm.$^{-1}$ in **8**; in general, of an epimeric pair of γ-butyrolactones, the more strained *trans* isomer absorbs at the higher frequency.[18,19]

The foregoing discussion clearly shows that the stereochemistry of C-7, C-8 and C-10 is as shown in **1**; the configuration of the C-6 oxygen and the C-11 methyl group is less certain. Originally,[3,17] the C-6 oxygen was placed so that it was *cis* to the C-7 side-chain. This assignment was made on the basis that not only was relactonization of ψ-santonin facile but also that such relactonization was specific with regard to the C-6 hydroxyl group. A stereochemical assignment on this basis when only one isomer is available is tenuous since there are *trans* lactones, *i.e.*, santonin, which form with great ease. In 1956, Cocker and his co-workers[7] reopened the question of this stereochemistry since they found that when ψ-santonin was heated with potassium hydroxide to 160°, conditions known to equilibrate the C-11



methyl group,[20,21] an iso-ψ-santonin was obtained in small yield. This transformation product was assigned structure **11** on the basis of its physical and chemical properties and it was concluded that such a structural change would only be expected if the original 6,12-lactone possessed *trans* stereochemistry. Since various results obtained in this Laboratory, and discussed below, strongly pointed to the correctness of the originally assigned *cis*-lactone arrangement, the structure of **11** was re-examined. It was found that the reaction product was a mixture of materials from which both ψ-santonin and iso-ψ-santonin could be isolated.[22] Upon oxidation with chromic acid in sulfuric acid and acetone, the iso-compound gave rise to a diketone which in the infrared possessed bands at 1772 (γ-lactone) and 1715 cm.$^{-1}$ (6-ring saturated ketone), the latter being about twice the intensity of the similar band in the starting material. In the ultraviolet above 220 mμ, the diketone showed only weak absorption at 290 mμ, characteristic of a saturated carbonyl system. When alkali was added, a strong maximum (ε 12,000) at 307 mμ developed. These spectral characteristics are incompatible with the structure **11** previously assigned to *iso*-ψ-santonin since a dione of structure **12** derived from it should show a maximum at 254 mμ and upon addition of base should yield **13** possessing similar

(18) J. H. Brewster and C. H. Kucera, THIS JOURNAL, **77**, 4564 (1955).

(19) T. Kanazawa, H. Kamio, M. Sumi and M. Nishikawa, *ibid.*, **80**, 3705 (1958).

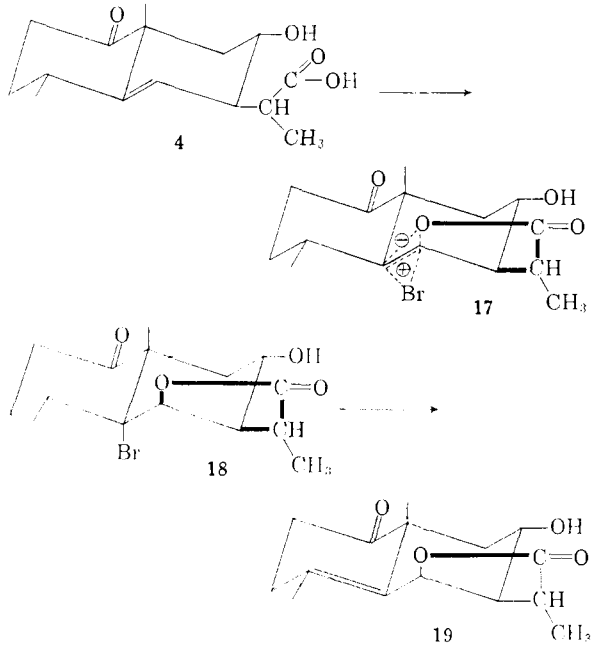
(20) Huang-Minlon, *ibid.*, **70**, 611 (1948).

(21) N. M. Chopra, W. Cocker and J. T. Edward, *Chemistry & Industry*, 41 (1955).

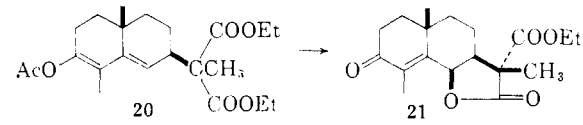
(22) If it be assumed that the crude reaction mixture consisted of only these two materials, the rotation indicated 60% ψ-santonin and 40% iso-ψ-santonin. The latter material upon hydrogenation yielded only oily acidic products. Although the acid could not be crystallized, its formation suggested the presence of an allylic lactone as in ψ-santonin and not an allylic alcohol as in **11**.

absorption. The structure **14** must be assigned to iso-ψ-santonin since such a material upon oxidation would yield the dione **15** with only isolated chromophoric groups and this material upon treatment with alkali would undergo β-elimination of the lactonic hydroxyl group to yield the dienone **16** which would possess a maximum at 305 mμ. This same reaction sequence has been used previously to establish the location of the hydroxyl group in ψ-santonin[3] and pyrethrosin[23] and the spectroscopic results parallel those reported above. Thus, the product from the potassium hydroxide fusion is an 11-iso-ψ-santonin and stereochemical arguments based upon structure 11 must be discounted.

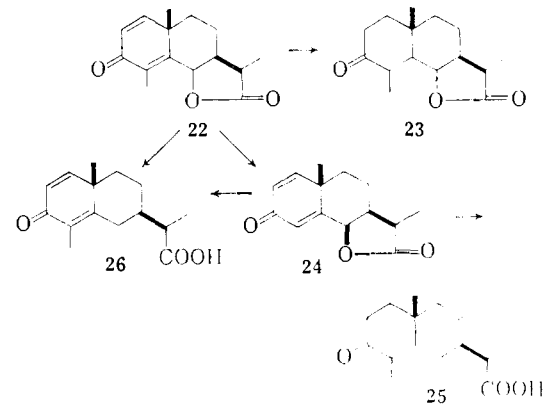
There are two series of experiments, however, which establish the *cis* nature of the lactone. First, it previously has been shown[4] that when 1-oxo-8α-oxysant-5-enic (**4**), the hydrogenolysis product of ψ-santonin, is converted to the bromo-lactone **18** and this, in turn, is dehydrobrominated, the product is ψ-santonin (**19**). In this reaction sequence, the stereochemistry of the lactone of **19** is fixed when the bromolactone **18** is prepared. The formation of



such a bromo-lactone is viewed[24] as proceeding *via* the transition state 17 involving *trans* addition of the carboxylate anion to the bromonium ion. An additional stereochemical feature of this transition state for a cyclic system stems from the well founded concept of *trans* diaxial electrophilic addition to a double bond.[25] As mentioned earlier, the angular methyl on C-10 possesses a so-called "β"-absolute configuration (above the plane of the projection) and it could be expected that the initial approach of bromine would be from the less hindered "α"-side (under side) of the molecule. If such be the case, *trans* diaxial addition demands that the resulting bromo-lactone possess the structure of a 5-bromo-6-hydroxy acid derivative, the structure previously shown to be correct. The stereochemical consequence of this reaction is that the oxygen function introduced at C-6 must possess a "β"-configuration and hence must be *cis* to the side-chain attached to C-7. In the closely related case of the synthesis of ethyl 11-carbethoxy-3-oxosant-4-en-6,12-olide (**21**) from the enol acetate **20** *via* a bromolactone, a *cis*-lactone was obtained and its mode of formation was pictured in a similar manner.[26]



The second series of experiments pointing to the *cis*-lactone structure pertains to the hydrogenation of isomeric lactones. One striking difference between ψ-santonin and (−)-α-santonin (**22**) is that the former upon hydrogenation undergoes hydrogenolysis to yield **4** while the latter yields the tetrahydro derivative **23** with the lactone intact. It is well established that the lactone in (−)-α-santonin is *trans* and the different course followed by the



hydrogenation reactions indicates that it may be controlled by stereochemical considerations. That such is the case was found by investigation of the same reaction with santonin-C (**24**), the *cis*-santonin prepared from **22** by isomerization with hydrogen chloride in dimethylformamide.[27] Santonin-C upon hydrogenation not only underwent reaction at the double bonds but also the lactone underwent hydrogenolysis to yield **25**. In both **22** and **24** the side-chain at C-7 is equatorial but the oxygen function at C-6 is equatorial in the former and axial in the latter. The different course followed by the two isomers suggests that hydrogenolysis is characteristic of an axial oxygen grouping. Since ψ-santonin also undergoes hydrogenolysis, an axial conformation of the C-6 oxygen function is indicated and with such a conformation only a *cis*-lactone is possible. The greater susceptibility to reductive cleavage of a *cis*-lactone possessing an axial oxygen function also has been found in the reaction of lactones **22** and **24** with zinc and acetic acid to yield (−)-α-desoxysantoninic acid (**26**)[28] and isohypoartemisin (**27**) to yield lactone **28**.[9]

(23) D. H. R. Barton and P. deMayo, *J. Chem. Soc.*, 150 (1957).

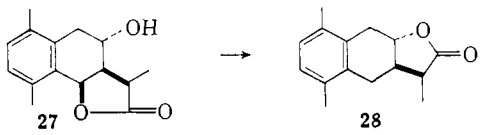
(24) R. T. Arnold, M. deMoura Campos and L. K. Lindsay, THIS JOURNAL, **75**, 1044 (1953); M. deMoura Campos, *ibid.*, **76**, 4480 (1954); E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954).

(25) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950).

(26) M. Sumi, *Pharm. Bull.* (*Tokyo*), **4**, 152 (1956).

(27) H. Ishikawa, *J. Pharm. Soc., Japan*, **76**, 507 (1956).

(28) T. Miki, *J. Pharm. Soc., Japan*, **75**, 412 (1955).



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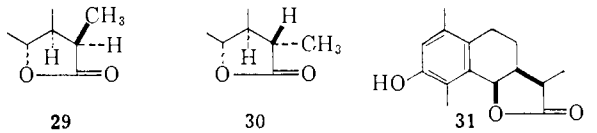
The last remaining stereochemical problem of ψ-santonin pertains to the configuration of the C-11 methyl group. In earlier work,[9] it has been shown that the configuration of this grouping in ψ-santonin is the same as in (−)-α-santonin. Although

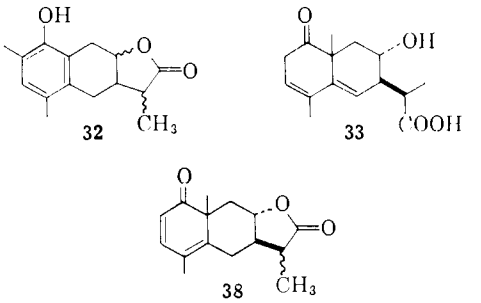


29 30 31

conflicting opinions exist as to the orientation of this methyl group,[21,29-34] the bulk of the evidence strongly favors **29** for (−)-α-santonin and **30** for (−)-β-santonin. This latter evidence stems mainly from the determination of the thermodynamically favored configurations of the epimeric desmotroposantonins (**31**) which possess *cis* lactones.[35,36] Recently, Cocker and McMurry[31,37] showed that if the lactone was of the *trans* series, the stable configuration of the C-11 methyl group was opposite to that in the *cis* series.[38] Assuming the configuration **29** for (−)-α-santonin, it follows that *the stable configuration of a* TRANS-*lactone is that in which the C-11 methyl group is* TRANS *to the C-7 hydrogen atom and of a* CIS-*lactone is that in which the groupings are* CIS *to one another.*[39]

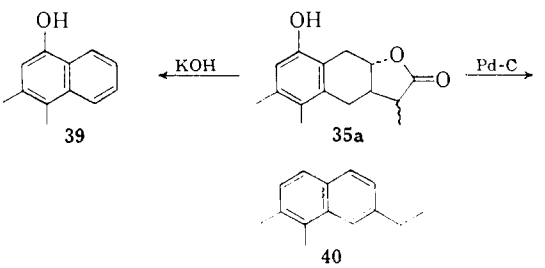
It has been reported by Cocker and his coworkers[7] that ψ-santonin is stable to potassium carbonate in boiling xylene,[40] a reagent which induces epimerization of the C-11 methyl group when it is in the unstable configuration. This result, coupled with the above rule of stable arrangements in *cis*-lactones, places the C-11 methyl group *cis* to the C-7 hydrogen or in the (−)-β-santonin configuration **30**, a conclusion which is just reverse from that arrived at on the basis of a direct interrelationship study.[9] In view of this discrepancy, the potassium carbonate epimerization was reinvestigated, and it was found that after 48 hours the rotation of the mixture had dropped from −156 to −135° and an additional 72 hours of reaction produced no further change. The total recovery of white crystalline material was high and after one recrystallization analytically pure material was obtained. No pure single component could be isolated. If it be assumed that the only reaction which occurred was the epimerization of the C-11 methyl group, then on the basis of rotation the equilibrium mixture contained 60% of ψ-santonin and 40% of 11-iso-ψ-santonin. Any such conclusion, however, is open to question since the presence of the hydroxyl group at C-8 offers a route for more extensive stereochemical changes.

To obtain unequivocal information with regard to this stereochemical problem, the chemistry of the desmotropo-ψ-santonins (**32**) was investigated. When either ψ-santonin or 1-oxo-8-oxysant-3,5-dienic acid (**33**) is allowed to react with 55% sulfuric



32 33 38

acid, the major product is (+)-β-desmotropo-ψ-santonin (**34**), and a very minor amount of an isomer, (+)-α-*iso*desmotropo-ψ-santonin (**35**), also is formed.[40] Both materials upon treatment with potassium carbonate in boiling xylene are cleanly epimerized to (+)-α-desmotropo-ψ-santonin (**36**) and (+)-β-isodesmotropo-ψ-santonin (**37**), respectively. The structure of **34** has been established[5,7] as being **32**, but **35** was assigned a similar structure possessing different stereochemistry on the basis of many similar chemical properties. If the rules given above regarding the stable configuration of a C-11 methyl group in a lactone are applicable to this 8,12-olide type of lactone (since the rules were derived for 6,12-olides), it is clear that since both **34** and **35** are unstable they must differ more than being lactones epimeric at C-8. An indication that these two materials differed in actual structure was gained when it was found that 1-oxosant-2,4-dien-8α,12-olide (**38**) upon reaction with 55% sulfuric acid gave rise to **34** and upon reaction in an anhydrous medium (acetic anhydride containing a trace of sulfuric acid) gave rise to the acetate of **35**. The dependency of the course of the dienone–phenol rearrangement upon the acidic catalyst is indicative that two different pathways are operable.[41] The structure of the (+)-α-iso compound **35** was shown



39 35a 40

(29) R. B. Woodward and P. Yates, *Chemistry & Industry*, 1391 (1954).

(30) E. J. Corey, THIS JOURNAL, **77**, 1044 (1955).

(31) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).

(32) W. Cocker and T. B. H. McMurry, *Chemistry & Industry*, 1430 (1956).

(33) T. Miki, *J. Pharm. Soc., Japan*, **75**, 416 (1955).

(34) Y. Abe, T. Miki, M. Sumi and T. Toga, *Chemistry and Industry*, 953 (1956).

(35) Huang-Minlon, THIS JOURNAL, **70**, 611 (1948).

(36) D. H. R. Barton, *J. Org. Chem.*, **15**, 469 (1950).

(37) W. Cocker, H. J. H. Dodds and T. B. H. McMurry, *Tetrahedron*, **3**, 160 (1958).

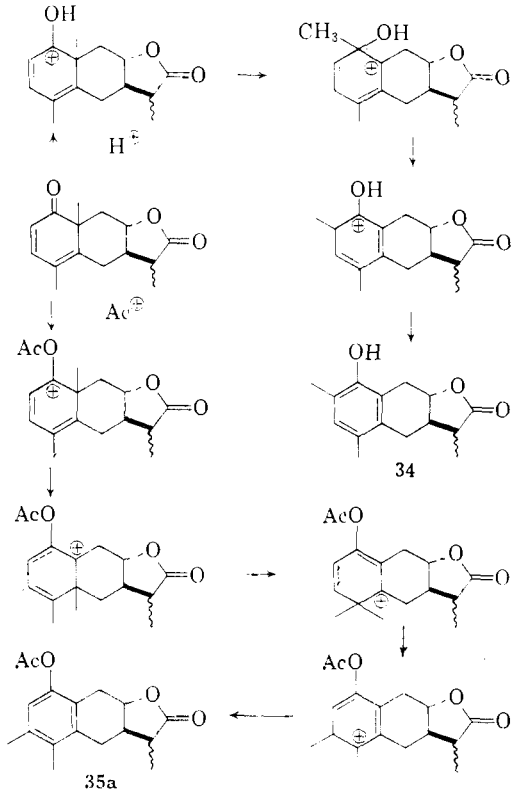
(38) Another example is the transformation of santonin-C (**24**) into santonin-D with potassium carbonate (M. Sumi, W. G. Dauben and W. K. Hayes, unpublished results).

(39) By examination of models, the stable configuration of a *cis*-lactone is quite apparent; with a *trans*-lactone, such is not the case.

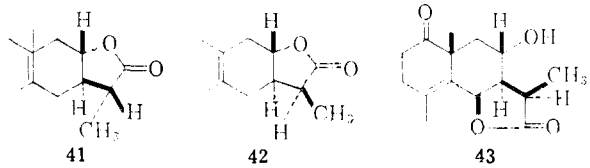
(40) W. Cocker, B. E. Cross and C. Lipman, *J. Chem. Soc.*, 959 (1949).

(41) A. S. Dreiding, W. J. Pummer and A. J. Tomasewski, THIS JOURNAL, **75**, 3159 (1953).

to be **35**a since upon fusion with potassium hydroxide it gave rise to 3,4-dimethyl-1-naphthol (**39**) and since upon dehydrogenation over Pd–C it gave rise to 1,2-dimethyl-7-ethylnaphthalene (**40**). The *trans*-lactone stereochemistry was assigned to **35**a since the material was derived from a *trans*-lactone and the reaction conditions employed in the preparation should not affect an isolated secondary hydroxyl function (in contrast to the ready inversion of the benzylic alcoholic functions in the desmotroposantonins).[31] The formation of the two desmotropo-ψ-santonins can be viewed as proceeding as shown below, the different products resulting from two different directions of migration of the C-10 methyl group which can lead to aromatic systems. It is of interest that in this series the spiranal intermediate which has been shown by Woodward[42] to be a favored intermediate in many dienenone–phenol rearrangements is not involved.



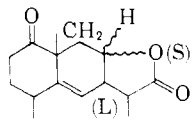
The establishment of the structure of (+)-α-isodesmotropo-ψ-santonin as **35a** now makes possible the determination of the configuration of the C-11 methyl group. Since both **34** and **35a** possess the same *trans*-lactone arrangement and the same C-11 methyl group configuration (that of ψ-santonin), it is to be expected that both materials should behave similarly toward potassium carbonate and, as pointed out above, both are epimerized by this reagent. Using the lactone rule pertaining to the stable configuration of the C-11 methyl group, the unstable series should be represented as **41** and the stable series as **42**. *It follows that ψ-santonin must possess the C-11 methyl configuration* of **41** and hence be represented as **43**. This formulation places the



C-11 methyl group in the same orientation as in (−)-α-santonin, a conclusion arrived at earlier on the basis of a direct correlation between the santonin and ψ-santonin series.[9]

The orientation of the C-11 methyl group in (−)-α-santonin (**29**), as mentioned earlier, was assigned on the basis of thermodynamic considerations. An alternate approach to this stereochemical problem has been taken by Bose and Chatterjee[43] who have formulated a generalized rule which permits the prediction of the absolute configuration of an asymmetric center. This rule states that of the two epimers, **44** and **45** (S = smaller group, L = larger group), the former will be less dextrorotatory. Using their compilations of relative sizes of groups (*i.e.*, C=O > —C—), Bose showed that the lac-

tones of the santonin series should possess the configurations assigned previously on the basis of thermodynamic studies. Application of this same rule to ψ-santonin (−156°), (+)-β-desmotropo-ψ-santonin (+68°) and (+)-α-isodesmotropo-ψ-santonin (+70) and their C-11 epimers (rotations −105°, +155°, +165°, respectively) yielded results which again suggest the stereochemical assignment for C-11 shown in **43**. Also, when the rule was employed with ψ-santonin (−156°) and 8-epi-ψ-santonin (−180°), the configuration of the C-8 hydroxyl function shown in **43** was found to be consistent with the rotational results. It was of interest also to test the rule on lactones **5** and **8** (rotations −248° and −73°, respectively). In such a fused ring lactone, there are two choices as to the peripheral substituents. As has been pointed out by Bose, in



such a case the carbocyclic ring and the hydrogen atom are considered as substituents and the lactone ring is considered as the basic cyclic structure. Following these assumptions, again agreement was obtained with regard to the assigned steric orientation of the C-8 oxygen function. This result was anticipated since the Bose–Chatterjee rule embraces the lactone rule of Klyne[12] which was used originally[7] to assign the C-8 orientation. The consistency of the rotational results obtained with the various transformation products, therefore, fits well with the concept assumed in the earlier discus-

(42) R. B. Woodward and T. Singh, THIS JOURNAL, **72**, 494 (1950).

(43) A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958); A. K. Bose, Abstracts of XVIth International Congress of Pure and Applied Chemistry, Paris, 1957, p. 141.

sion that the C-11 methyl configuration remains constant except when reactions involving strong basic conditions are employed.

During the course of this investigation, Kanazawa, Kamio, Sumi and Nishikawa[19] reported a study of the infrared spectra of santonin isomers and they called attention to two characteristic bands in the 1200-900 cm.$^{-1}$ region. They showed that by consideration of the position and intensity of these bands the stereochemical configuration of the lactone could be determined. The infrared spectra of **5**, **8**, **34**, **35**, **36** and **43** were obtained under conditions used by these workers and no such systematic correlation was apparent. The only feature which the two series possessed in common was that the major band in the 950–1050 cm.$^{-1}$ region appeared above 1000 cm.$^{-1}$ when the lactone was *trans* and below this value when the lactone was *cis*.

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Experimental[44]

1-Oxosant-5-en-8β,12-olide (8).—ψ-Santonin tosylate (7.58 g., 19.1 mmoles) dissolved in 300 ml. of ethanol was added to 7.5 g. of prehydrogenated 10% Pd–$SrCO_3$ catalyst suspended in 100 ml. of ethanol. The mixture was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure until the hydrogen uptake ceased [472 ml. (19.0 mmoles) absorbed in 10 minutes]. The mixture was filtered, the filtrate poured into 4.5 l. of saturated sodium bicarbonate solution and the solution allowed to stand overnight at room temperature. The bicarbonate solution then was extracted with methylene chloride, the organic phase dried and the solvent removed. The residual crude lactone (4.0 g.) was recrystallized from benzene–ligroin; yield 3.0 g. (67%), m.p. 123.5–124.5°, $[\alpha]^{25}D$ −73.0° (*c* 1.52, EtOH).

Anal. Calcd. for $C_{15}H_{20}O_3$ (248.31): C, 72.55; H, 8.12. Found: C, 72.52; H, 8.07.

8-Epi-ψ-santonin (10).—1-Oxosant-5-en-8β,12-olide (3.0 g., 12.1 mmoles) was dissolved in 90 ml. of 1% sodium hydroxide solution by heating on a steam-bath for 30 minutes. The solution was cooled in an ice-bath and carbon dioxide was bubbled through it until the *p*H was 8. Then, 1.8 g. (11.2 mmoles) of bromine in 90 ml. of water was added dropwise to the swirled solution. The precipitated bromolactone (1.7 g.) was collected by filtration, air-dried for 4 hours and dehydrobrominated by heating at 135° for 3 hours in 26 ml. of 2:1 collidine–toluene. The cooled reaction mixture was diluted with methylene chloride, extracted 4 times with 3 *N* hydrochloric acid, washed with water and dried. The solvent was evaporated at reduced pressure and the residue recrystallized from chloroform–benzene; yield 0.36 g. (14%), m.p. 179.5–181.0°, $[\alpha]^{25}D$ −185° (*c* 1.1, $CHCl_3$ or EtOH).

Anal. Calcd for $C_{15}H_{20}O_4$ (264.31): C, 68.16; H, 7.63. Found: C, 68.19; H, 7.50.

11-Iso-ψ-santonin (14).—The preparation of the material was achieved, in varying yields, by utilization of a combination of purification techniques. The course of the separation of the isomers was followed, in part, by examination of the crystalline form, the starting material appearing as cubes and the 11-iso compound as needles.

ψ-Santonin (3.0 g., 11.4 mmoles) was dissolved in 6 ml. of water containing 6.0 g. of potassium hydroxide and the solution heated at 160° for 4 hours. The dark brown mixture was poured into 50 ml. of ice-water, the solution acidified with hydrochloric acid and the mixture extracted 4 times with methylene chloride. The combined extracts were washed with 5% sodium bicarbonate solution, which removed most of the discoloration, water and dried. Upon evaporation of the solvent, 2.25–2.6 g. (75–85%) of nearly colorless crystalline material was obtained, $[\alpha]^{25}D$ −137° (*c* 1.3, EtOH). The product was recrystallized 4 times from large volumes of benzene so as to ensure only partial recovery and there was obtained 0.185 g. of impure 11-iso-ψ-santonin as white needles, m.p. 196–202°. This material was combined with other preparations of similar purity and the purification described below.

The benzene mother liquor from the first recrystallization was evaporated slowly and the 1.4 g. of slightly yellow solid obtained was dissolved in benzene and placed on a chromatographic column containing 55 g. of Florex XXS. Upon elution with benzene containing 2% and then 5% acetone there was obtained 0.6 g. of slightly impure ψ-santonin. Two recrystallizations from benzene gave 0.30 g. of pure material as prisms, m.p. 187.5–189.0° (lit.[4] 189.8–190.8). Upon further elution with 9:1 benzene–acetone there was obtained 0.15 g. of solid which upon recrystallization from benzene deposited needles of impure 11-iso-ψ-santonin. Elution with 4:1 benzene–acetone yielded 80 mg. of material which upon recrystallization from benzene gave nearly pure 11-iso compound, m.p. 212–215°.

Two samples of impure 11-iso-ψ-santonin (0.11 g., m.p. 195–204°; 0.185 g., m.p. 196–202°) obtained from the recrystallization of original reaction product were combined and chromatographed on 11 g. of Florex XXS. Elution with 19:1 benzene–acetone first yielded a total of 0.185 g. of material with a m.p. less than 200°. The later fractions with this same solvent combination and the first fractions eluted with 9:1 benzene–acetone gave a total of 70 mg. of white needles. Recrystallization of the last fraction yielded 20 mg. of pure material as well-formed needles, m.p. 219–220°, $[\alpha]^{25}D$ −104.3° (lit.[7] m.p. 205°, $[\alpha]D$ −110°).

Anal. Calcd. for $C_{15}H_{20}O_4$ (264.31): C, 68.16; H, 7.63. Found: C, 68.35; H, 7.56.

By repetition of these processes, combined with manual separation of cubes and needles, additional amounts of the 11-iso material were obtained.

11-Iso-1,8-dioxosant-4-en-6β,12-olide (15).—To 0.135 g. (0.51 mmole) of 11-iso-ψ-santonin in 5 ml. of acetone (freshly distilled from potassium permanganate) was added 0.2 ml. (0.53 mmole) of 2.67 *M* CrO_3 in sulfuric acid and the mixture allowed to stand at room temperature for 30 minutes. After filtration to remove chromium salts, the acetone solution was diluted with 25 ml. of water and extracted 4 times with methylene chloride. The methylene chloride solution was washed with water, dried over magnesium sulfate and the solvent evaporated. The crude dione (0.13 g., 97%, m.p. 153–160°) was recrystallized from ethanol–water (plates); m.p. 156.0–158.5°; ultraviolet spectrum: λ_{max} 298 mμ (ε 260); in 0.1 *M* ethanolic potassium hydroxide, λ_{max} 307 mμ (ε 12,000).

Anal. Calcd. for $C_{15}H_{18}O_4$ (262.29): C, 68.68; H, 6.92. Found: C, 67.62; H, 6.39.

Hydrogenation of Santonin-C.—To 0.4 g. of prehydrogenated 5% palladium-on-charcoal in 20 ml. of glacial acetic acid was added 2.00 g. (8.1 mmoles) of (−)-santonin C in 60 ml. of acetic acid and the mixture hydrogenated at room temperature and atmosphere pressure until the hydrogen uptake ceased. After 28 minutes, 23.2 mmoles of hydrogen had been consumed. The catalyst was filtered, the solvent evaporated and the residue dissolved in methylene chloride. The organic solution was extracted with 5% sodium bicarbonate solution, the methylene chloride layer dried and the solvent removed. The residual neutral material (1.15 g., 57%) was recrystallized twice from ethanol–water; yield 0.15 g. (7%) of tetrahydrosantonin C, m.p. 165.5–166.5°, $[\alpha]^{25}D$ −114° (*c* 0.8, EtOH).

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.33): C, 71.97; H, 8.86. Found: C, 71.50; H, 8.70.

Acidification of the sodium bicarbonate extract yielded an oil (0.77 g., 38%) which could not be obtained crystalline. The acidic material was characterized as the oxime, m.p. 192.0–193.0° dec., and the 2,4-dinitrophenylhydrazone, m.p. 185.5–187.0° dec.

Anal. Calcd. for $C_{15}H_{25}O_3N$ (267.37): C, 67.38; H, 9.34; N, 12.97. Found: C, 67.47; H, 9.16; N, 5.03. Calcd. for $C_{21}H_{28}O_6N_4$ (432.47): C, 58.32; H, 6.53; N, 12.97. Found: C, 59.09; H, 6.53; N, 12.97.

Under the same reaction conditions, (−)-α-santonin absorbed 2.0 moles of hydrogen per mole of lactone and no acidic material could be detected.

(44) All analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

Potassium Carbonate Isomerization of ψ-Santonin.—A mixture of 1.5 g. (5.67 mmoles) of ψ-santonin and 4.0 g. of freshly ignited potassium carbonate was refluxed in 45 ml. of *p*-xylene under a nitrogen atmosphere and 4-ml. aliquots were removed after 2 and 5 days. Both samples had $[\alpha]^{20}D$ −133.5° (*c* 1.1, $CHCl_3$). After a total of 7 days, the heating was discontinued and 1.3 g. of only slightly discolored crystalline material was recovered, $[\alpha]^{20}D$ −137° (*c* 1.1, $CHCl_3$). The product was recrystallized from benzene–ligroin; m.p. 153–164°, $[\alpha]^{20}D$ −140° (*c* 1.2, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{20}O_4$ (264.31): C, 68.16; H, 7.63. Found: C, 68.50; H, 7.65.

If it be assumed that this material is a binary mixture of ψ-santonin ($[\alpha]D$ −156°) and 11-iso-ψ-santonin ($[\alpha]D$ −105°), then there is 60% of the former and 40% of the latter.

(+)-α-Isodesmotropo-ψ-santonin Acetate (35).—A solution of 3.12 g. (12.7 mmoles) of 1-oxosant-2,4-dien-8β,12-olide in 70 ml. of acetic anhydride was treated with 12 drops of sulfuric acid dissolved in 5 ml. of acetic anhydride. The resulting solution was allowed to stand at room temperature for 15 hours, and then was cooled in an ice-bath. The crystalline product was filtered and washed with small portions of ethanol; yield 1.64 g. (45%), m.p. 246–248°, $[\alpha]^{21}D$ + 69.4° (*c* 1.1, $CHCl_3$) (lit.[40] m.p. 244.5–245.5°, $[\alpha]^{20}D$ + 64.1° [*c* 0.4, $CHCl_3$]); ultraviolet spectrum: λ_{max} 267 mμ (ε 380), 273 mμ (ε 330), 276 mμ (ε 335).

Anal. Calcd. for $C_{17}H_{20}O_4$ (288.33): C, 70.81; H, 6.99. Found: C, 70.88; H, 6.74.

(+)-α-Isodesmotropo-ψ-santonin (35).—A solution of 1.64 g. (5.70 mmoles) of the above acetate, 11 g. of potassium hydroxide and 50 ml. of methanol was heated under reflux for 4 hours. The solution was poured into 400 ml. of water and then acidified with hydrochloric acid. The acid solution was heated for 15 minutes to promote lactonization. The crude product precipitated as a white powder and, after cooling, the mixture was filtered; yield 1.32 g. (94%), m.p. 245–253°, $[\alpha]^{24}D$ + 70.3 (*c* 0.60, $CHCl_3$) (lit.[40] m.p. 251–253°, $[\alpha]^{20}D$ + 68.5° [*c* 0.71, $CHCl_3$]); ultraviolet spectrum: λ_{max} 285 mμ (ε 2270).

Anal. Calcd. for $C_{15}H_{18}O_3$ (246.29): C, 73.14; H, 7.37. Found: C, 73.00; H, 7.61.

3,4-Dimethyl-1-naphthol from 35.—(+)-α-Isodesmotropo-ψ-santonin acetate (855 mg., 3.96 mmoles) was stirred and warmed with 5.0 ml. of water and 835 mg. of potassium hydroxide until a clear solution was obtained. The temperature of the solution was gradually increased to 230° at which point no more water vapor was observed above the fused mass. The temperature then was increased rapidly to 320° and the reaction mixture held at this temperature for 10 minutes. When the fused mass had cooled, it was washed with water into a distillation flask and then directly steam distilled. Colorless crystals were filtered from the distillate; yield 153 mg. (30%), m.p. 123–124°. The product was recrystallized from ligroin–chloroform; yield 102 mg. (20%), m.p. 124–125° (lit.[45–47] m.p. 121–123°).

Anal. Calcd. for $C_{12}H_{12}O$ (172.22): C, 83.69; H, 7.02. Found: C, 83.97; H, 7.32.

The naphthol coupled with diazotized aniline to form a red dye. The ultraviolet spectrum showed λ_{max}^{EtOH} 211 mμ (ε 39,300), 240 mμ (ε 39,300), 305 mμ (ε 5,200), 330 mμ (ε 1,930). Cocker and co-workers[47] report λ_{max} 242 mμ (ε 27,000), 306 mμ (ε 7,800), 330 mμ (5,400).

3,4-Dimethyl-1-naphthyl Acetate.—A solution of the above prepared 3,4-dimethyl-1-naphthol (22.7 mg., 0.132 mmole), 3.0 ml. of acetic anhydride and 3 drops of pyridine was heated under reflux for 7 hours. It then was poured into 60 ml. of water and the solid material which formed was filtered; yield 19 mg. (67%), m.p. 88–90°. Recrystallization from ethanol–water gave 6.3 mg. of dimorphic material, m.p. 79–80°. This latter material was dissolved in 15 drops of hot 95% ethanol and after the solution cooled slightly a seed crystal of the higher melting dimorph was added and the product allowed to crystallize, m.p. 89.5–90.5°, undepressed upon admixture with an authentic sample.[48]

Dehydrogenation of (+)-α-Isodesmotropo-ψ-santonin (35).—A sealed tube containing 790 mg. (3.21 mmoles) of (+)-α-isodesmotropo-ψ-santonin and 740 mg. of 10% palladium-on-charcoal was heated at 250–265° for 48 hours. After a short period of heating, liquid refluxed in the tube. The organic material was extracted from the tube with 4 portions of hot methanol. The combined extracts were filtered and concentrated; yield 320 mg. The residue was dissolved in chloroform and the solution washed with 2 *N* sodium hydroxide and water. The solvent was removed and the residue dried to constant weight, 300 mg. The oily material was dissolved in 15 ml. of chloroform and the resulting solution was treated in the following manner:

(a) A 5.0-ml. aliquot was added to 141 mg. of trinitrotoluene and the solution then concentrated to a dark yellow oil which solidified on standing. The solid material was recrystallized from methanol to yield 83 mg. of the trinitrotoluene derivative of 1,2-dimethyl-7-ethylnaphthalene as lemon-yellow needles, m.p. 88.0–90.5° (lit.[49] lemon-yellow needles, m.p. 88–89°).

Anal. Calcd. for $C_{21}H_{21}O_6N_3$ (411.40): C, 61.25; H, 5.15; N, 10.21. Found: C, 60.97; H, 4.86; N, 10.71.

(b) A 5.0-ml aliquot was added to 146 mg. of picric acid and the solution processed as above to yield 52 mg. of the picric acid derivative of 1,2-dimethyl-7-ethylnaphthalene as orange needles, m.p. 105–107° (lit.[49] orange needles, 104–105).

Anal. Calcd. for $C_{20}H_{19}O_7N_3$ (413.38): C, 58.11; H, 4.63; N, 10.17. Found: C, 57.97; H, 4.86; N, 10.71.

A sample of the hydrocarbon was obtained by chromatography of the picric acid derivative on alumina using petroleum ether–benzene (1:1) as the eluent. The ultraviolet spectrum of the material showed λ_{max}^{EtOH} 277 mμ (ε 5,000), 284 mμ (ε 5,100), 320 mμ (ε 290) [lit.[49] λ_{max} 270 mμ (ε 4,070), 281 mμ (ε 4,880), 319 mμ (ε 270).

The alkaline extracts of the reaction mixture upon acidification yielded about 10 mg. of a crude material which could not be characterized.

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