first one has the same intensity and appears at the same frequency as with heyderiol and apparently stems from the hydroxyl in position 1[10]; the second less intensive one corresponds accordingly to the hydroxyl in position 4. With the concentrated solutions and with the melt there appears, in addition, a strong band resulting from the unresolved hydrogen bond bands of the hydroxyls. With its maximum at 3380 cm.$^{-1}$ (melt) it is shifted to the longer wave length in respect to the hydrogen bond band of heyderiol. Taking this value, one calculates 0.68 for the hydrogen bonding index of hydroxyl in position 4. This is a minimum value since, due to poor resolution, the actual position of the band in question might be at still slightly lower frequency.

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(10) Demethylation of a para methoxyl does not seem to influence the position of the free hydroxyl stretching. L. L. Ingraham, J. Corse, G. F. Bailey, F. Stitt, *J. Am. Chem. Soc.*, **74**, 2297 (1952).

All measurements were made at room temperature using hexachlorobutadiene and iso-octane as solvents. For calculation of the concentrations the specific weight of hexachlorobutadiene has been measured as 1.68 at 22°; the specific weights of the phenols used were assumed to be equal to that of *p*-methoxythymal (1.03 at 24°).[10]

Santonin and Related Compounds. XVIII.[1] Tetrahydro-β-santonins[2]

MASAITI YANAGITA AND HARUO OGURA

In addition to the two known tetrahydro compounds (IIBa and IIBb) of β-santonin, two new stereoisomers (IIBc and IIBd) have been obtained. The former isomers were of *trans*-decalin type, and the latters of *cis*-decalin type. IIBa and IIBc were readily isomerized into IIBb and IIBd, respectively. The reverse conversion in each pair of the ketones was effected by hydrolysis of IIBb or IIBd and subsequent relactonization of the resulting acid (IIIBa or IIIBc) under mild conditions. From these results, the four tetrahydro ketones were assigned the stereoformulas (VIIB → XB). On heating with sodium methoxide, the 3-desoxy compound (VBb) from IIBb was converted to VAb under epimerization of the methyl group at the 11-position.

A number of papers[3] concerning the preparation of the tetrahydro derivatives of α-santonin (IA) and the elucidation of their stereochemistry have been published in recent years. Of four possible stereoisomers of these compounds, three (IIA, IIAb, and IIAd) are recorded,[4] and in their stereoformulas the configurations at all the asymmetric centers

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(1) Part XVII, S. Inayama, *J. Org. Chem.*, **23**, 1183 (1958).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955). (b) B. Riniker, thesis, E. T. H. Zürich, 1955. (c) O. Kovacs, V. Herout, M. Herak, and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956). (d) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956). (e) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956). (f) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956). (g) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956). (h) M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

(4) The synthesis of the fourth isomer of the tetrahydro compound has been achieved, and will be published in a later communication of this series.

(5) (a) For example see R. B. Woodward and P. Yates, *Chem. & Ind. (London)*, 1391 (1954): *Cf.* M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958). (b) Y. Abe, T. Miki, M. Sumim, and T. Toga, *Chem. & Ind. (London)*, 953 (1956); and references cited there. (c) W. Cocker and T. B. H. McMurry, *Chem. & Ind. (London)*, 1430 (1956).

appear acceptable, except two at the 4-[3f] and 11-position; the latter is the same as in α-santonin.[5] For the purpose of comparison, β-santonin (IB), which is epimeric at the 11-position with α-santonin, was catalytically hydrogenated under similar conditions to the tetrahydro derivatives. Isolation of each isomer of these compounds and assignment of its stereoformula will be recorded in this paper.

It has been stated by Clemo[6] that β-santonin was hydrogenated over palladium-charcoal in acetic acid to two stereoisomers of tetrahydro compounds, m.p. 207–208° (a) and m.p. 125–126° (b), in 25% and 30% yields, respectively. Also it has been disclosed that the use of ethanol in place of acetic acid afforded only the low-melting isomer-b in 66% yield. On repetition, these results were found to be reproducible. To avoid confusion, the previous designations "a" and "b" for these tetrahydro derivatives (IIBa and IIBb, respectively) were employed in this paper. In order to obtain other possible isomers of the tetrahydro compounds (IIB), hydrogenation of β-santonin was explored with a variety of catalysts and of reaction media. When the hydrogenation was carried out over palladium-charcoal in acetone containing either traces of hydrochloric acid or a small amount of methanol, only the isomer-b (IIBb) was obtained in satisfac-

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(6) G. R. Clemo, *J. Chem. Soc.*, 1343 (1934).

tory yield. On the other hand, use of absolute ace-tone alone in this system afforded predominantly the other isomer-a in 57% yield. On hydrogenation over platinic oxide in dry benzene, the yield of the isomer-a was raised to 70%. It is noteworthy that in the above hydrogenation, the reduced polarity of the solvent favors the isomer-a, which is less stable than the isomer-b, as described below.

It has been reported by Cocker and McMurry[3f] that when the sodium salt of α-santoninic acid, a lactone-opening product of α-santonin (IA), was hydrogenated over platinum black in aqueous alkaline solution, the salt of the cis-fused tetrahydro acid (IIIAc) was obtained as the chief product. By application of this procedure, sodium β-santoninate was reduced over Raney nickel in methanolic alkaline solution, and about two equivalents of hydrogen were absorbed rather rapidly. The crude product was acidified and then heated to completely reform the lactone ring, and after chromatography on alumina, there were obtained two new tetra-hydro compounds, m.p. 203–205° and m.p. 139–140°, in 6% and 35% yields, respectively. The former, the melting point of which is close to that of the isomer-a but depressed on admixture with it, is tentatively designated as the tetrahydro ketone-c (IIBc) and the latter isomer as the ketone-d (IIBd). Beside these two isomers, the ketones-a and -b (IIBa and IIBb) were isolated, both in small yields, from the less readily eluted fractions after chromic acid oxidation. When the acidification of the crude hydrogenation products was not followed by external heating, a tetrahydro acid of m.p. 205–206°, together with the ketone-b (IIBb), was obtained in low yield. This acid was tentatively designated as the tetrahydro acid-c (IIIBc). In the alkaline hydrogenation system, substitution

of Raney nickel by platinic oxide furnished pre-dominantly the acid-c, accompanied by another acid of the same melting point in 14% yield. These two were easily differentiated by the depressed mixture melting point and the comparison of rotatory powers. The new acid (IVBc) was lacto-nized to the dihydro ketone-d (VIBd), which was quantitatively hydrogenated over palladium-char-coal in methanol to the tetrahydro ketone-d (IIBd). The Δ^1-structure (VIBd) for this dihydro ketone can be assigned on the basis of its ultra-violet spectrum, λ_{max}^{EtOH} 226 mμ (log ε 3.96), char-acteristic of α,β-unsaturated ketones with one sub-stituent.[7] Further support for this structure was found in the infrared spectrum which showed the shift (26 cm.$^{-1}$) of the carbonyl band over that of the ketone-d (IIBd).[8]

Clemo[6] has shown that both tetrahydro ketones-a and -b (IIBa and IIBb) were reduced by the Clem-mensen method to the same 3-desoxy compound (VBb). From this fact, it may be inferred that, of two asymmetric centers newly formed on hydro-genation of IB, one at the 10-position which ap-pears quite stable to acid possesses the same con-figuration in these two ketones. Therefore, they must differ in the spatial arrangements of the methyl group at the 4-position which is epimeriz-able, being in a position α to the carbonyl group. It has been established[3] that catalytic hydrogena-tion of α-santonin in a neutral medium led pref-erentially to the trans-fused tetrahydro ketones (IIAa or VIIA and IIAb or VIIIA), while in a basic medium the cis-isomer (IIAd or XA) is favored.[3f] On analogy with these results, it may be assumed that the fusion of two six-membered rings is trans in the ketones-a and -b (IIBa and IIBb), and cis in the ketones-c and -d (IIBc and IIBd). Hence, the 3-desoxy compound (VBb) cited above should have a trans-relationship of these rings. On warming with dilute ethanolic hydrochloric acid, the ke-tones-a and -c were readily converted to the iso-mers-b and -d, respectively. These isomerizations, which apparently involve inversion of the labile methyl group at the 4-position, indicates that this methyl group is axial in the former ketones, and equatorial in the latter two. It follows that the ketones-a, -b, -c, and -d (IIBa, IIBb, IIBc, and IIBd) can be represented by the stereoformulas VIIB, VIIIB, IXB, and XB, respectively. These assignments are in line with those of the cor-responding ketones, β, α, and γ[3a,9] (VIIA, VIIIA,

IA
IB

IIAa,b,d
IIBa,b,c,d

IIIAa,c
IIIBa,c

IVBc

VAb,d
VBb,d

VIBd
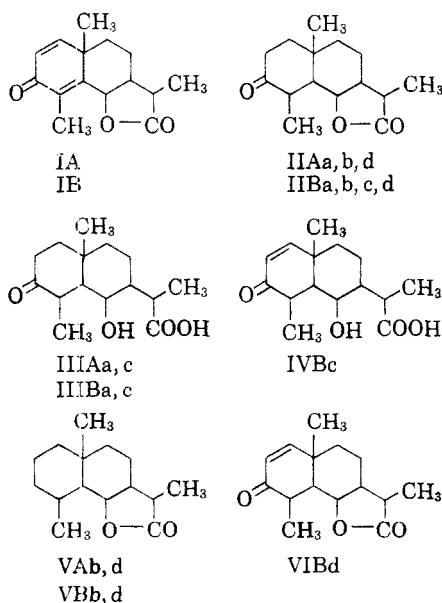
A: α-Santonin series
B: β-Santonin series

(7) L. F. Fieser and M. Fieser, Natural Products Related to Phenanthrene, 3rd ed., Reinhold Publishing Corp., New York, 1947, p. 190.

(8) F. A. Miller in Gilman's Organic Chemistry, An Ad-vanced Treatise, John Wiley & Son, Inc., New York, 1953, Vol. III, p. 152.

(9) For the definition of the nomenclature and the num-bering used in this paper, see Part XIII of this series (reference 13).

CH₃ ... VIIA VIIB ... CH₃ ... VIIIA VIIIB ... IXA IXB ... XA XB

A: α-Santonin series
B: β-Santonin series
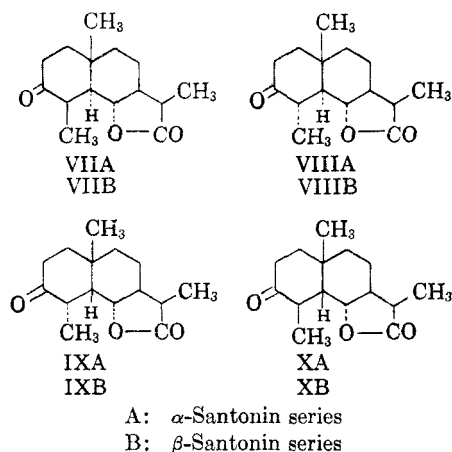
and XA) in the α-santonin series, but IXB is now lacking in its epimer (IXA).[4]

It has been reported[10] that β-santonin was epimerized to α-santonin by refluxing with potassium carbonate in xylene. This reaction could be duplicated by use of the commercial reagents, but when the reagents were cautiously dried, β-santonin was substantially recovered unchanged. It is possible that this epimerization occurred with opening of the lactone ring. By the same procedure an attempt was made to transform the above 3-desoxy compound (VBb) into its epimer of the α-santonin series, but it remained unaffected. However, this transformation was readily effected by heating VBb with sodium methoxide in methanol at 170–180°. The product, obtained in 80% yield, was identified as the 3-desoxy compound (VAb), prepared previously from α-tetrahydro-α-santonin (IIAb) by the Clemmensen method.[3c,11] This result gave conclusive evidence for the trans-fusion of the six-membered rings in the ketones-a and -b (VIIB and VIIIB). It is notable that in the β-santonin molecule, complete hydrogenation of the dienone ring caused the methyl group of the α-propionic acid residue to be more stable. The relative stability of VBb may be attributed to the effect of the release of strain on saturation of the dienone ring, forming a rigid skeleton of trans-decalin type. Attempt to effect similar epimerization of the 3-desoxy derivative (VBd), prepared from the ketone-d (IIBd) by the same Clemmensen procedure, failed. The configuration of this methyl group in the compounds of α- and β-santonin series will be discussed below.

Recently, Cocker and McMurry[3f] have disclosed an interesting finding about the stereochemistry of γ-tetrahydro derivative (IIAd) of α-santonin. The cis-fused tetrahydro santoninic acid (IIIAc), described above, was lactonized by heating to give γ-tetrahydro ketone (IIAd), which on treatment

(10) W. Cocker and T. B. H. McMurry, J. Chem. Soc., 4430 (1955).
(11) E. Wedekind and K. Tettweiler, Ber., 64, 387 (1931).

with alkali regenerated IIIAc. It was suggested by these workers that since these compounds were reduced to the different hydroxy lactones under similar conditions, they must differ in the configurations of the labile methyl group at the 4-position. This procedure of the interconversion was extended to the tetrahydro compounds in the β-santonin series. The cis-tetrahydro ketone-d (IIBd) was treated with warm dilute alkali to give a hydroxy acid-c (IIIBc), which gave back the ketone-d on heating with dilute hydrochloric acid. This result parallels the interconversion between IIAd and IIIAc. Moreover, it was found in this work that brief treatment of the hydroxy acid (IIIBc) with cold concentrated sulfuric acid gave rise to the ketone-c (IIBc) in almost quantitative yield. It is of interest that the conversion of the ketone-d into ketone-c through IIIBc involves a net conversion of the equatorial methyl group at the 4-position into the axial conformation. With a view of the work of Cocker and McMurry,[3f] it is apparent that this inversion has occurred in the stage of the lactone opening. Similarly, the trans-ketone (IIBb) was readily converted to the less stable isomer (IIBa) through the acid-a (IIIBa).

Cocker and McMurry[3f] assigned the methyl groups at the 4-position in the above acid (IIIAc) and the ketone (IIAd) equatorial and axial positions, respectively. The latter orientation (corresponding to IXA) is the reverse of that suggested previously (XA).[3] These assignments are based mainly on the assumption that catalytic hydrogenation of α-santonin into the γ-ketone (XA) involves 1,2-β-addition of hydrogen to the double bond, which requires the introduced hydrogen atoms at the 4- and 10-positions to be cis with respect to each other. This argument does not seem valid. Contrary to their opinion, α- and β-santonins, as described above, were catalytically hydrogenated in a neutral medium to furnish fair amounts of tetrahydro compounds, in which the newly entered hydrogen atoms at the referred positions stand in a trans-relationship. It seems that the labile methyl group at the 4-position in the initial hydrogenation products from santonins or santoninic acids could be inverted to the more stable conformation during hydrogenation even in a neutral medium or during the isolation of the products.

The steric aspect of the above interconversion between the trans-fused ketones-a and -b (IIBa and IIBb) may be reasonably explained in terms of their stereoformulas (VIIB and VIIIB) proposed in the present work. The more stable ketone-b, which can be described by the conformation XI, would initially form a hydroxy acid (XII) on hydrolysis. Examination of the molecular models indicates that in XI, opening of the lactone ring causes a closer proximity of the two equatorial substituents at the 4- and 5-positions. The resulting interaction between these groups, which is associated with the

"4,5-effect",[12] is equivalent in strength to that of the *meta*-diaxial effect, as stated previously.[13] In combination with the 2-methyl ketone effect,[14] this compression may force the methyl group at the 4-position into the axial position to give the observed acid-a (XIV), in opposing the newly formed repulsion between the two axial methyl groups.[15]
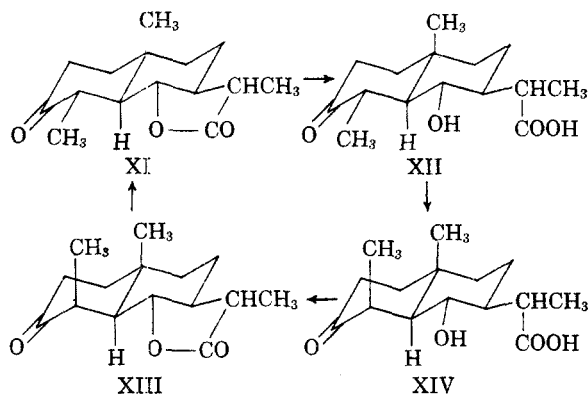
These steric factors resemble closely those suggested for explanation of the relative stabilities of epimers of 30-nortaraxastan-20-ones in which the axial methyl group at the 19-position is favored over the equatorial one.[16] It is obvious that lactonization of the acid-a (XIV) under mild conditions forms the ketone-a (XIII) which readily regenerates the more stable isomer (XI). The interconversion between the *cis*-fused ketones-c and -d (IXB and XB) is presumed to involve a similar steric aspect, but because of complexity of conformational analysis of these formulas, it is difficult to assess the relative stabilities of these ketones. An effort to establish the steric aspects in the interconversions of the tetrahydro ketones (IIA and IIB) is now being made in this laboratory.

In conclusion, we should like to discuss the configurations of the methyl group at the 11-position in α- and β-santonins. The above cited epimerization of the 3-desoxy compound (VBb) into VAb possibly occurs under cleavage of the lactone ring. The hydroxy acid resulting from V can be partially described, respectively, by the most favorable
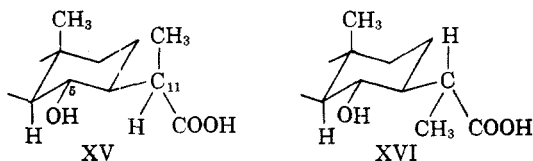
(12) W. Klyne, *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. 1, p. 53.

(13) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958) (Paper XIII of this series).

(14) W. Klyne, *Experientia*, **12**, 119 (1956).

(15) When the preparation of this manuscript was being made, J. C. Banerji, D. H. R. Barton, and R. C. Cookson [*J. Chem. Soc.*, 5041 (1957)] have published almost the same opinion on the conformational analysis of the tetrahydro derivatives in α-santonin series.

(16) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

conformation XV or XVI, in which the ring carbon at the 5-position and the carboxyl group are as far apart as possible. Examination of molecular models shows that, of these two structures, XV is sterically more favored than XVI by one less *meta*-diaxial interaction between the hydroxyl group at the 5-position and the methyl group at the 11-
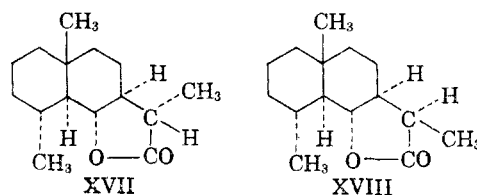
position. It follows that VAb and VBb must be represented by the stereoformulas XVII and XVIII, respectively. This gave strong support for the revised configurations of the methyl group in α- and β-santonins (IA and IB), which are the same as in XVII and XVIII respectively.

EXPERIMENTAL[17]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube, unless otherwise noted.

β-Santonin (IB). This was obtained from "santonin residues" of Carnegies of Welwyn Limited (Welwyn Garden City, Hertfordshire, England). The residues, white crystals, m.p. 142–147°, were washed with chloroform to remove α-santonin, and recrystallized from ethanol to give in 50–60% yield β-santonin as white plates, m.p. 215°, $[\alpha]_D^{18}$ −140.0° (c 0.20; $CHCl_3$) and $[\alpha]_D^{24}$ −138.2° (c 0.43; EtOH); λ_{max}^{EtOH} 240 mμ (log ε 4.09). Reported,[5] m.p. 216–218°, $[\alpha]_D^{19}$ −137.5° ($CHCl_3$). With Brady's reagent,[13] it formed quantitatively a *2,4-dinitrophenylhydrazone*, which was recrystallized from chloroform-methanol (1:1) to deep red fine needles, m.p. 258°; $\lambda_{max}^{CHCl_3}$ 258 mμ (log ε 4.15) and 395 mμ (log ε 4.44).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20; N, 13.14. Found: C, 58.95; H, 5.27; N, 13.33.

Catalytic hydrogenation of β-santonin (IB) *in a neutral or acidic medium.* (a) By an effective modification of the method reported by Clemo,[6] β-santonin was converted to the tetrahydro compounds (IIB). β-Santonin (IB, 0.85 g.) was hydrogenated in the presence of 4% palladium-charcoal (0.2 g.) in 10 cc. of glacial acetic acid. About 2 molar-equivalents (165 cc.) of hydrogen was absorbed within 30 min. and the gas uptake ceased. After filtration of the catalyst, the reaction solution was evaporated to a small volume, and a little ethyl acetate was added. There was obtained 0.21 g. (24.2%) of the *tetrahydro ketone-a* (IIBa), m.p. 197°. Further recrystallization from ethyl acetate furnished plates, m.p. 209–210°; $[\alpha]_D^{24}$ +131.8° (c 0.22; EtOH, 1-dm. tube); $\nu_{C-O}^{CHCl_3}$ 1770 cm.$^{-1}$ and $\nu_{C-O}^{CHCl_3}$ 1704 cm.$^{-1}$ Reported, m.p. 207–208°.[6]

The mother liquor of crystallization of IIBa was evaporated to a small volume, and a little ethanol was added. On standing, 0.15 g. (17.3%) of the *tetrahydro ketone-b* (IIBb), separated as white plates, m.p. 95–100°. Recrystallization from dilute ethanol raised the melting point to 125–126°. Reported, 125–126°.[6] The mother liquor from the recrystallization of IIBb gave a sirup, which afforded an additional 0.09 g. (total 27.7%) of IIBb, m.p. 123°, after warming with dilute hydrochloric acid in ethanol.

(b) β-Santonin (IB, 0.50 g.) was hydrogenated over 0.10 g. of 3% palladium-charcoal in 20 cc. of acetone containing one drop of concentrated hydrochloric acid. About 2 molar-equivalents (88 cc.) of hydrogen was absorbed within 15 min. After filtration of the catalyst, the filtrate was evaporated under reduced pressure to leave a colorless sirup, which gave 0.35 g. (68.6%) of *tetrahydro-β-santonin-b* (IIBb), m.p. 113°, from an ether solution by addition of petroleum ether. Further recrystallization from dilute ethanol forms colorless plates, m.p. and mixed m.p. 125°; $[\alpha]_D^{14}$ +84.3° (c 1.6: CHCl$_3$); $\nu_{C-O}^{CHCl_3}$ 1764 cm.$^{-1}$ and $\nu_{C-O}^{CHCl_3}$ 1704 cm.$^{-1}$

A *semicarbazone*, obtained in 97% yield, was recrystallized from ethanol to colorless prisms, m.p. 241° (decomp.).

Anal. Calcd. for C$_{16}$H$_{23}$N$_3$O$_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.57; H, 8.51; N, 13.84.

With Brady's reagent, it formed in 70% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to fine yellow needles, m.p. 222–223°; $\lambda_{max}^{CHCl_3}$ 364.5 mμ (log ϵ 4.40) and 300 mμ (log ϵ 3.37).

Anal. Calcd. for C$_{21}$H$_{26}$N$_4$O$_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.55; H, 5.82; N, 13.00.

(c) β-Santonin (2.00 g.) was hydrogenated over 0.2 g. of 9% palladium-charcoal in a mixture of 50 cc. of acetone and 15 cc. of methanol. Hydrogen (400 cc., 2.2 molar-equivalents) was absorbed. Worked up as above, the residual sirup furnished the ketone (IIBb, 1.04 g.) m.p. 112°, from an ethanol solution by addition of a little water. Recrystallization from dilute ethanol afforded 0.93 g. of colorless plates, m.p. and mixed m.p. 123°. The sirup, obtained from the mother liquor of IIBb, was warmed with dilute hydrochloric acid in methanol to give an additional 0.50 g. (total 70.4%) of IIBb, m.p. and mixed m.p. 123°.

(d) The hydrogenation of IB (2.00 g.) was carried out under the same conditions as described above in (c), except only dry acetone (50 cc.) was used instead of the mixture of solvents. Hydrogen (420 cc., 2.3 molar-equivalents) was absorbed. After removal of the catalyst, the solution was evaporated under reduced pressure to a small bulk, giving 1.15 g. (57%) of the *tetrahydro ketone-a* (IIBa), colorless plates, m.p. 200°. Recrystallization from ethyl acetate gave colorless plates, m.p. and mixed m.p. 207°.

(e) β-Santonin (IB, 0.50 g.) was hydrogenated over platinic oxide (0.03 g.) in dry benzene (20 cc.), and absorption of about 2 molar-equivalents (100 cc.) of hydrogen required 5 hr. On working up as described in (d), the *ketone-a* (IIBa, 0.21 g., 41%), m.p. 204°, was obtained. Recrystallization from ethyl acetate afforded colorless plates, m.p. and mixed m.p. 212°: $[\alpha]_D^{26}$ +116.0° (c 4.0; CHCl$_3$). The mother liquor from the crystallization gave additional 0.15 g. (total 70%) of IIBa, m.p. 188°.

It forms quantitatively a *semicarbazone*, which was recrystallized from ethanol to fine white needles, m.p. 255° (decomp.): $[\alpha]_D^{16}$ −25.3° (c 0.48; pyridine).

Anal. Calcd. for C$_{16}$H$_{25}$N$_3$O$_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.90; H, 7.79; N, 13.38.

With Brady's reagent, it was converted in 76.4% yield to the 2,4-dinitrophenylhydrazone of the ketone-b (IIBb), which was recrystallized from ethyl acetate to yellow fine needles, m.p. and mixed m.p. 221°.

Hydrogenation of β-santonin (IB) *in basic medium.* (a) β-Santonin (IB, 0.50 g.) was dissolved in warm alkali solution (0.5 g. of potassium hydroxide in 10 cc. of methanol and 1 cc. of water), and the clear solution was shaken under an atmosphere of hydrogen in the presence of Raney nickel (prepared from 3 g. of alloy) until the gas absorption was complete. In 3 hr., 110 cc. (2.4 molar-equivalents) of hydrogen was consumed. After removal of the catalyst, the solution was evaporated under reduced pressure, and the residual oil was warmed with concentrated hydrochloric acid to reform the lactone ring and then was taken up in ether. Evaporation of the dried ether solution gave a colorless oil (0.48 g.) which was chromatographed on alumina (15 g.). The elution with petroleum ether–benzene (3:2) afforded 0.18 g. (35%) of the *tetrahydro ketone-d* (IIBd), colorless

plates, m.p. 135–136°. Recrystallization from the same solvent mixture and then from dilute ethanol raised the melting point to 139–140°; $[\alpha]_D^{19}$ +71.1° (c 0.90; CHCl$_3$); $\nu_{C-O}^{CHCl_3}$ 1767 cm.$^{-1}$ and $\nu_{C-O}^{CHCl_3}$ 1701 cm.$^{-1}$ It showed obvious depression of the melting point (98–100°) on admixture with the above ketone-b (IIBb), m.p. 125–126°.

Anal. Calcd. for C$_{15}$H$_{22}$O$_3$: C, 71.97; H, 8.86. Found: C, 71.65; H, 8.63.

It formed in 82% yield a *semicarbazone*, which was recrystallized from ethanol to fine colorless needles, m.p. 215° (decomp.).

Anal. Calcd. for C$_{16}$H$_{25}$N$_3$O$_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.48; H, 8.25; N, 13.79.

With Brady's reagent, IIBd gave in 60% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized to golden yellow plates, m.p. 194°; $\lambda_{max}^{CHCl_3}$ 365 mμ (log ϵ 4.26) and 300 mμ (log ϵ 3.20).

Anal. Calcd. for C$_{21}$H$_{26}$N$_4$O$_6$: C, 58.59; H, 6.09. Found: C, 58.52; H, 6.25.

The following fractions eluted with benzene gave 0.03 g. (6%) of the *tetrahydro ketone-c* (IIBc), m.p. 147°. Recrystallization from benzene afforded white needles, m.p. 198° and mixed m.p. 200° with a sample (IIBc) described below. It was converted to the ketone-d (IIBd) with 2,4-dinitrophenylhydrazine or with acid, which will be described below in more detail.

The last fractions eluted with methanol furnished a colorless sirup (0.25 g.), which could not be crystallized. The sirup was oxidized with chromic acid–pyridine, and from the neutral fraction, 0.08 g. (16%) of IIBa, m.p. 200°, which was recrystallized from ethanol to colorless prisms, m.p. and mixed m.p. 209–210°. A sirup from the mother liquor of IIBa was dissolved in a little ethanol, and a little water was added. On standing in a refrigerator, 0.04 g. (8%) of IIBb separated as white plates, m.p. 120°, which was raised by recrystallization from dilute ethanol to 123° (mixed melting point).

(b) As described above in (a), β-santonin (5.00 g.) in potassium hydroxide solution (5.0 g. of potassium hydroxide in 40 cc. of methanol and 20 cc. of water) was hydrogenated in the presence of Raney nickel (from 15 g. of alloy). About 2 molar-equivalents (1000 cc.) of hydrogen were absorbed, and the oily product was mixed with concentrated hydrochloric acid and the mixture, which was not externally heated, was extracted with ethyl acetate. The acetate solution was shaken with aqueous bicarbonate, and was evaporated to leave a sirup (3.08 g.) which solidified partly. The residue (1.52 g.) was chromatographed on alumina (50 g.), and the elution with petroleum ether–benzene (4:1) furnished the *ketone-b* (IIBb) as crude crystals (0.63 g.), melting in the range 75–105°. Recrystallization from dilute ethanol gave colorless plates, m.p. and mixed m.p. 124°.

The bicarbonate solution, removed from the neutral fraction, was acidified and extracted with ethyl acetate. Evaporation of the ethyl acetate solution left a sirup (2.00 g.), which solidified partly. From a methanolic solution by addition of water, the sirup gave 0.85 g. (16%) of the *hydroxy acid-c* (IIIBc) as colorless needles, m.p. 198°. Recrystallization from dilute ethanol raised the melting point to 204–206°; $[\alpha]_D^{28}$ +9.05° (c 2.87; EtOH).

Anal. Calcd. for C$_{15}$H$_{24}$O$_4$: C, 67.13; H, 9.02. Found: C, 67.04; H, 8.66.

(c) Hydrogenation of β-santonin (IB, 5.00 g.) was carried out under the same conditions as described in (b), except platinic oxide (0.16 g.) was used as catalyst in place of Raney nickel. About 2 molar-equivalents (929 cc.) of hydrogen were absorbed. The acid fraction, a sirup (4.00 g.) which solidified partly, gave 0.75 g. (14%) of the Δ^1-*dihydro acid* (IVBc), colorless prisms, m.p. 203–205°, from a methanol solution by addition of water. Recrystallization from dilute ethanol raised the melting point to 204–206°; $[\alpha]_D^{28}$ −54.8° (c 1.93; EtOH) and $[\alpha]_D^{28}$ −33.2° (c 3.13; pyridine). It showed obvious depression (about 20°) of the melting

point on admixture with the tetrahydro acid-c (IIIBc), m.p. 204–206°, described above.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.68; H, 8.33. Found: C, 67.69; H, 8.49.

Catalytic hydrogenation of IVBc with palladium-charcoal in methanol afforded quantitatively the tetrahydro acid-c (IIIBc), m.p. 198°. A pure sample showed m.p. and mixed m.p. 204° (from dilute ethanol).

The mother liquor of crystallization of IVBc gave 1.50 g. (27%) of the *acid-c* (IIIBc), m.p. 198°, which on recrystallization from dilute ethanol showed m.p. and mixed m.p. 203–204°. A colorless sirup (1.6 g.), obtained from the mother liquor of IIIBc, was chromatographed on silica gel (20 g.), and the elution with benzene–ethyl acetate (7:3) afforded additional 0.33 g. (total 32%) of IIIBc, m.p. 195°.

The neutral fraction, a colorless sirup (1.10 g.) was dissolved in warm 10% potassium hydroxide, and the clear solution was acidified with cooling. After standing at room temperature for 5 hr., the separated oil was extracted with ethyl acetate and the dried acetate solution was evaporated to leave a sirup (0.75 g.), which deposited 0.26 g. of white needles, m.p. 154°, from an ethanol solution by addition of water. Further recrystallization from dilute ethanol raised the melting point to 165°, undepressed on admixture with the tetrahydro acid-a (IIIBa) described below.

Δ¹-*Dihydro-β-santonin* (VIBd). The Δ¹-dihydro acid (IVBc, 0.75 g.), described in the preceding paragraph, was refluxed with *p*-toluenesulfonic acid (0.05 g.) in 50 cc. of benzene for 5 hr. After washing with aqueous bicarbonate and then water, the solution was dried and evaporated to leave 0.69 g. (99%) of the Δ¹-*dihydro-β-santonin* (VIBd) as colorless plates, m.p. 157°. Recrystallization from ethanol raised the melting point to 158–159°; $[\alpha]_D^{28}$ +31.7° (c 3.53; $CHCl_3$); λ_{max}^{EtOH} 226 mμ (log ε 3.96); $\nu_{C=O}^{CHCl_3}$ 1675 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.40; H, 8.09.

With Brady's reagent, it formed almost quantitatively a *2,4-dinitrophenylhydrazone*, which was recrystallized from methanol-chloroform to fine yellow needles, m.p. 204°; $\lambda_{max}^{CHCl_3}$ 258 mμ (log ε 4.44) and 375 mμ (log ε 4.75).

Anal. Calcd. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.54; H, 5.76; N, 13.25.

Catalytic hydrogenation of the dihydro ketone (VIBd, 0.03 g.) with 5% palladium-charcoal (0.01 g.) in methanol (5 cc.) resulted in a quantitative yield (0.03 g.) of the tetrahydro ketone-d (IIBd), m.p. 130°. Recrystallization from dilute ethanol raised the melting point to 140° (mixed m.p.).

Hydroxy acid-a (IIIBa) *from the tetrahydro ketone-b* (IIBb). The ketone-b (IIBb, 0.10 g.) was added to 10 cc. of 5% aqueous sodium hydroxide, and the mixture was warmed on a water bath for 1.5 hr. After cooling, the clear solution was washed with ether, acidified with 5% dilute hydrochloric acid under ice cooling, and extracted with ethyl acetate. Evaporation of the dried acetate solution furnished 0.07 g. (65%) of the acid-a (IIIBa), m.p. 144°. Recrystallization from dilute ethanol gave white needles, m.p. 165°; $[\alpha]_D^{22}$ −51.6° (c 1.24; EtOH).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.92; H, 8.65.

Acid treatment of the hydroxy acid-a (IIIBa). (a) *With cold concentrated sulfuric acid.* The powdered acid-a (IIIBa, 0.01 g.), above described, was added to concentrated sulfuric acid with ice cooling, and was dissolved to a clear solution in about two minutes. Immediately, the solution was poured into ice water, and the separated solid was taken up in ether. The ether solution was washed with aqueous sodium bicarbonate and then with water. Evaporation of the dried ether solution left 5 mg. (54%) of the pure ketone-a (IIBa) as colorless plates, m.p. and mixed m.p. 209°.

(b) *With dilute hydrochloric acid on heating.* A solution of the above acid-a (IIIBa, 0.03 g.) in methanol (1 cc.) and 5% hydrochloric acid (1 cc.) was heated to reflux for 1 hr.

On cooling, the solution deposited 0.02 g. (71%) of the ketone-b (IIBb) as colorless plates, m.p. 120°. A pure sample had m.p. and mixed m.p. 125–126° (from dilute ethanol).

Isomerization of the ketone-a (IIBa) *to the ketone-b* (IIBb). A solution of the ketone-a (IIBa, 0.05 g.) in ethanol (3 cc.) containing 3% hydrochloric acid (0.5 cc.) was warmed for 30 min. on a water bath. On cooling, the solution deposited the ketone-b (IIBb, 0.035 g., 70%), m.p. 123°. A pure sample had m.p. and mixed m.p. 124–125° (from dilute ethanol).

Hydroxy acid-a (IIIBc) *from the tetrahydro ketone-d* (IIBd). The hydrolysis of IIBd (0.02 g.) was carried out as described above for IIBb, giving the acid-c (IIIBc, 0.015 g., 72%), m.p. 198°. Recrystallization from benzene afforded colorless leaflets, m.p. and mixed m.p. 204–206°; $[\alpha]_D^{28}$ +9.74° (c 1.23; EtOH).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.27; H, 9.14.

Acid treatment of the hydroxy acid-c (IIIBc.) (a) *With cold concentrated sulfuric acid.* As described above for IIIBa, the acid-c (IIIBc, 0.33 g.) was treated with concentrated sulfuric acid (1.5 cc.) and the ketone-c (IIBc, 0.29 g., 94%) was obtained as colorless plates, m.p. 160°. Recrystallization from ethyl acetate raised the melting point to 205°; $[\alpha]_D^{17}$ +26.3° (c 0.53; $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1764 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ It showed obvious depression (*ca.* 20°) of the melting point on admixture with the starting acid-c.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.73; H, 8.90.

A *semicarbazone*, obtained in 81% yield, was recrystallized from ethanol afforded white crystalline powder, m.p. 258° (decomp.).

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: N, 13.67. Found: N, 13.73.

With Brady's reagent, it forms in 60% yield a 2,4-dinitrophenylhydrazone, m.p. 192° and mixed m.p. 193°, of the ketone-d (IIBd).

(b) *With dilute hydrochloric acid on heating.* As described above for IIIBa, the acid-c (IIIBc, 0.90 g.) was heated with 5% hydrochloric acid (30 cc.) and methanol (10 cc.) to regenerate the ketone-d (IIBd, 0.78 g., 93%) as colorless plates, m.p. 133°. Recrystallization from dilute ethanol raised the melting point to 138–139° (mixed m.p.).

(c) *With p-toluenesulfonic acid.* The acid-c (IIIBc, 0.15 g.) was refluxed with *p*-toluenesulfonic acid (0.01 g.) in benzene (12 cc.) for 5 hr. After cooling, the mixture was washed with aqueous sodium bicarbonate, then dried and evaporated to give the ketone-d (IIBd, 0.13 g., 92%) as colorless plates, m.p. 135–137°. Recrystallization from dilute ethanol raised the melting point to 139–140° (mixed m.p.).

Isomerization of the ketone-c (IIBc) *to the ketone-d* (IIBd). As described above for IIBa, the ketone-c (IIBc, 0.02 g.) was converted with hydrochloric acid to the ketone-d (IIBd, 0.015 g.), colorless plates, m.p. 133°. A pure sample showed m.p. and mixed m.p. 139° (from dilute ethanol).

3-Desoxytetrahydro-β-santonin-b (VBb). This was prepared from the ketone-b (IIBb) by a slight modification of the procedure previously reported.[6] The ketone-b (0.50 g.) in 1 cc. of toluene was heated to reflux for 24 hr. with zinc amalgam (prepared from 1.2 g. of zinc and 0.05 g. of mercuric chloride) in 1.7 cc. of concentrated hydrochloric acid and 1 cc. of water. One half cc. each of concentrated hydrochloric acid was added to the refluxed reaction 2 times during a period of 4 hr. After cooling, ether was added to the reaction mixture, and the organic layer was separated, washed with water, dried, and evaporated. There was obtained 0.40 g. (85%) of the 3-desoxy compound-b (VBb) as colorless prisms, m.p. 72°. Recrystallization from petroleum ether raised the melting point to 76°; $[\alpha]_D^{17}$ +87.6° (c 1.67; EtOH). Reported, m.p. 75–76°.[6]

Isomerization of the 3-desoxy compound-b (VBb) *to* VAb. The above desoxy compound (VBb, 0.15 g.) was added to sodium methoxide solution (from 5 cc. of 99% methanol

and 0.5 g. of sodium metal), and was heated in a sealed tube at 170–180° for 2 hr. After cooling, the solution was diluted with water, acidified with hydrochloric acid, and warmed for 15 min. on a water bath. The solution was extracted with ether, and the ether solution was washed with aqueous bicarbonate, dried, and evaporated to leave 0.12 g. (80%) of colorless leaflets, m.p. 150°. Recrystallization from dilute ethanol raised the melting point to 153°; $[\alpha]_D^{18}$ +21.9° (c 2.47; EtOH). It showed no depression of the melting point on admixture with 3-desoxy-α-tetrahydro-α-santonin (VAb)[3b,c] m.p. 154°; $[\alpha]_D^{21}$ +20.8° (c 0.87; EtOH), prepared from IIAb by the Clemmensen reduction.

3-Desoxytetrahydro-β-santonin-d (VBd). By the Clemmensen method described above for preparing VB, the ketone-d (IIBd, 0.29 g.) was reduced to an oily product, which was fractionated to a colorless oil (VBd, 0.22 g., 80%), b.p. 73–75° at 3 mm. The oil (0.17 g.) was chromatographed on alumina (10 g.), and the elution with petroleum ether-benzene (2:1) gave 0.13 g. of colorless sirup, which solidified almost completely; m.p. 88–89°; $[\alpha]_D^{19}$ +60.0° (c 1.27; CHCl$_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.35; H, 10.01.

Attempt on isomerization of VBd into the corresponding compound (VAd)[3c] in α-santonin series by the procedure described for VBb was unfruitful.

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Derivatives of (+)-Limonene. I. Esters of *trans-p*-Menthane-1,2-diol[1]

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The hitherto unreported diacetate, dipropionate and dibutyrate esters of trans-p-menthane-1,2-diol have been synthesized from (+)-limonene in 50 per cent yield. Partial hydrogenation of (+)-limonene followed by hydroxylation with performic acid affords a crystalline mixture of *trans-p*-menthane-1,2-diols in 60 per cent yield. The diols are converted in 90–95 per cent yield to the diesters by reaction with the appropriate acid anhydride.

This paper describes a convenient synthesis of *trans-p*-menthane-1,2-diol and three of its diester derivatives. The preparation of *trans-p*-menthane-1,2-diol by the hydrogenation of *trans*-$\Delta^{8(10)}$-*p*-menthene-1,2-diol has been reported by Schmidt[2] and others.[3] Improved yields of this saturated diol have been obtained in this laboratory by first hydrogenating the exocyclic double bond of (+)-limonene and then hydroxylating the endocyclic double bond by reaction with performic acid.

Hydrogenation of freshly distilled (+)-limonene[4] (I) without solvent, at low pressure, over a 5 per cent platinum on Darco G-60 catalyst proceeds smoothly to afford Δ^1-*p*-menthene (II) in virtually quantitative yield. It is imperative to use only freshly distilled material, because the catalyst is rapidly poisoned by compounds (probably peroxides) formed in (+)-limonene stored in contact with air for as short a period as five days. The hydrogenation is highly exothermic and absorption of hydrogen almost ceases when one mole has been absorbed per mole of (+)-limonene. It has been found practicable to use the same catalyst for as many as thirty consecutive hydrogenations. Spent catalyst is easily reactivated by washing with acetone and drying for one hour at 110°. This ease of partial hydrogenation of (+)-limonene was first described by Vavon,[5] who used a heat deactivated platinum catalyst. More recently Fujita and Matsuura[6] accomplished the same partial hydrogenation using Adams' platinum catalyst in methanol solution.

Hydroxylation of Δ^1-*p*-menthene (II) by the gradual addition of one equivalent of preformed performic acid followed by hydrolysis of the intermediate monoformate esters with alcoholic potassium hydroxide, affords a crystalline mixture of *trans-p*-menthane-1,2-diols (III) in 60% over-all yield from (I). Direct addition of II to the performic acid solution results in yields of III 20–25% less than obtained by the inverse addition procedure. Separation of the diols III by fractional crystallization affords 40–45% of one diol melting at 89° and 8–12% of another diol melting at 55°. By analogy with the work of Jefferies and Milligan[7] and Cole and Jefferies,[8] on the racemic *trans-p*-menthane-1,2-diols, the higher melting, more abundant diol probably has the conformation of their compound (I) (1-hydroxyneocarvomenthol) and the lower melting diol corresponds in structure to

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