[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY, UNIVERSITY OF CALIFORNIA]

Extractive Components from Incense Cedar Heartwood (*Heyderia decurrens* Torrey). VII. On the Occurrence of Heyderiol

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A new cryptophenolic compound, heyderiol, $C_{22}H_{30}O_4$, has been isolated from incense cedar heartwood in 0.14% yield (dry wood basis). It contains one phenolic hydroxyl, two methoxyls, and one ether oxygen. Oxidation with ferric chloride gave heyderioquinone, which, in turn, was oxidized with alkaline hydrogen peroxide to *p*-methoxycarvacrol. This elucidated the structure of the nonquinoidal part of the quinone. Demethylation of heyderiol, followed by oxidation with ferric chloride produced nonheyderioquinone, which upon pyrolysis gave 3-hydroxythymoquinone. This identified the quinoidal part of the heyderioquinone. Oxidation of the mixture of *p*-methoxythymol and *p*-methoxycarvacrol with alkaline ferricyanide produced heyderiol in addition to the expected libocedrol. Since coupling of this kind takes place normally in *o* or *p* positions to the hydroxyl, it would appear that heyderiol is 6-*p*-methoxycarvacroxy-*p*-methoxythymol.

The determination of the structure of heyderiol adds another member to the group of compounds with *p*-cymene carbon skeleton found in incense cedar heartwood, interrelated through enzymatic oxidation.

In continuing our investigation of the nature of the extractive components present in the heartwood of incense cedar (*Heyderia*[1] *decurrens* Torrey), the mother liquors from the separation of the libocedrol/*p*-methoxythymol addition complex[2] have been examined. Steam distillation removed the volatile portion leaving the nonvolatile residue amounting to 1.1% (dry wood basis), which was partially soluble in 10% sodium hydroxide solution. The insoluble portion amounted to 0.57% (dry wood basis) and represented a viscous, reddish liquid. *p*-Nitrobenzoylation and crystallization of the reaction product gave a sharply melting yellow *p*-nitrobenzoate in 0.14% yield (dry wood basis). Hydrolysis of this ester with alcoholic alkali gave a white, crystalline powder, m.p. 62.2–63.2°.

The isolated material, heyderiol (I), analyzed correctly for $C_{22}H_{30}O_4$, was optically inactive and contained two methoxyl groups. The C-CH_3 determination pointed out the presence of at least four methyls bonded to carbon. The elemental analysis of the *p*-nitrobenzoate ester substantiated the empirical formula and indicated that we are dealing with the monoester; determination of the molecular weight by the Rast camphor method also gave a value in agreement with this formula.

Heyderiol reacted with bromine in carbon tetrachloride solution with evolution of hydrogen bromide, slowly gave a red color with alcoholic ferric chloride, but was insoluble in sodium hydroxide solutions. This seems to point out its cryptophenolic nature.

The ultraviolet absorption spectrum of heyderiol was practically identical with the absorption spectrum of libocedrol[2] with the benzenoid B-band appearing at 287 mμ. In the infrared a sharp peak at 3520 cm.$^{-1}$ was present, stemming from the free OH stretching. No carbonyl band was detected. (Figs. 1 and 2.)

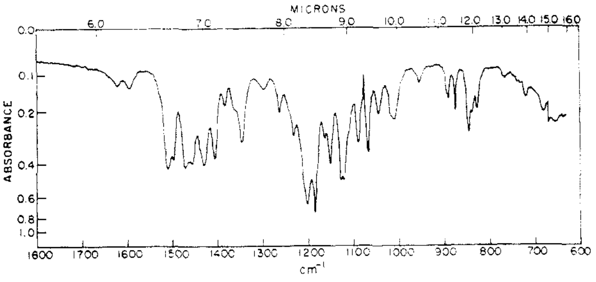

Fig. 1. Infrared absorption spectrum of heyderiol in the 1800–600 cm.$^{-1}$ region

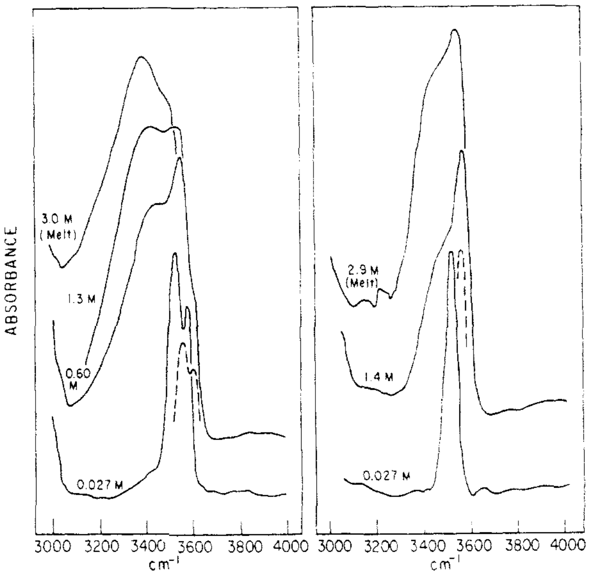

Fig. 2. Infrared absorption spectra in the 3000–4000 cm.$^{-1}$ region of hydroheyderioquinone (left) and heyderiol (right) in hexachlorobutadiene (———) and iso-octane (---------) solutions of various concentrations and in the melt form.

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[1] According to the new classification by Li; *Libocedrus decurrens* Torrey according to the older classification. See H. L. Li, *J. Arnold Arboretum* (*Harvard Univ.*), **34,** 17 (1953).

[2] E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20,** 788 (1955).

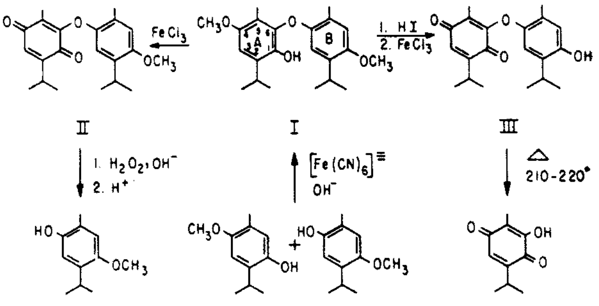
Oxidation of heyderiol with alcoholic ferric chloride gave heyderioquinone (II), $C_{21}H_{26}O_4$, containing one methoxyl. The ultraviolet absorption spectrum of this quinone was very similar to that of libocedroquinone. It exhibited the quinoid bands with maxima at 260 mμ (A-band), 363 mμ (B-band), and 455 and 475 mμ (C-band) together with an inflection point at 284–285 mμ, resulting from the benzenoid B-band of the second, unoxidized aromatic nucleus. Applying Braude's rules[3] for the position of the absorption bands, it was possible to determine that the quinoid part of the molecule should be oxygen substituted in at least one position. The calculated positions were 262 mμ for A-band and 361 mμ for B-band. The infrared spectrum of the heyderioquinone was also very similar to that of libocedroquinone; it exhibited no bands in the OH region; possessed, however, strong bands corresponding to the conjugated carbonyl and conjugated double bond stretchings at 1660 and 1615 cm.$^{-1}$, respectivly. The NMR spectrum (40 mc.) was also reminiscent of that of libocedroquinone with three peaks in the aromatic region (-1.45, -1.30, -1.15 parts per million), corresponding to the three aromatic hydrogens, a peak at $+1.3$ parts per million corresponding to the methyl of the methoxy group, two peaks corresponding to the aromatic methyls ($+2.70$, $+3.00$ parts per million) and the isopropyl doublet ($+3.80$, $+3.95$ parts per million). The intensities of the peaks agreed with the above assignments.

The results of the analyses, chemical and optical behavior, and the general nature of structure present in incense cedar heartwood seem to strongly suggest that we are dealing with a libocedrol-type compound formed through oxidative coupling of two *p*-methoxythymol or *p*-methoxycarvacrol units.

Oxidation of heyderioquinone with alkaline hydrogen peroxide and heating the reaction product with dilute sulfuric acid resulted in formation of *p*-methoxycarvacrol, identified by mixed melting point and infrared techniques. This establishes the structure of ring B of heyderioquinone.

Demethylation of heyderiol with hydriodic and acetic acid mixture and oxidation of the resulting product with ferric chloride produced norheyderioquinone, $C_{20}H_{24}O_4$ (III). Pyrolysis of the latter resulted in formation of 3-hydroxythymoquinone, identified with the synthetically prepared material by mixed melting point and comparison of the infrared spectra. This establishes the structure of the ring A of heyderioquinone.

The above degradative transformations do not determine which of the two ring A hydroxyls is methylated in heyderiol. As reported in one of the previous publications, the alkaline ferricyanide oxidation of *p*-methoxythymol produced libocedrol.[4] When an analogous reaction was carried out using the mixture of *p*-methoxythymol and *p*-methoxycarvacrol, in addition to the expected libocedrol, heyderiol also could be isolated from the reaction mixture. The identity of the synthetic heyderiol with the naturally occurring compound was established by mixed melting point and infrared techniques. Since the ferricyanide coupling of the phenols takes place ortho or para to the hydroxyl, this synthesis seems to establish that in heyderiol the 4 hydroxyl is methylated, as the occurrence of the methoxyl in the 1 position would involve meta coupling of the two *p*-methoxycarvacrol units.



The occurrence of the methoxyl in ring A in 4 position has been substantiated also spectroscopically. It has been known that ortho substitution of the phenols exerts marked influence on the hydrogen bonding in solution. This effect can be studied best in the infrared where the shift from free hydroxyl stretching frequency (dilute solutions in nonpolar solvents) to the frequency of the hydroxyl engaged in hydrogen bonding (concentrated solutions or melts) is related to the strength of the hydrogen bonds. Sears and Kitchen[5] have defined hydrogen bonding indices to serve as a measure of this effect.

It is clear that a hydroxyl in position 1 should be susceptible to weaker hydrogen bonding than hydroxyl in position 4, due to the increased steric hindrance. The hydrogen bonding index for heyderiol has been determined from the infrared spectra, to be about 0.30; the same index for the free hydroxyl in position 4 could be estimated from the spectra of hydroheyderioquinone (prepared by the reduction of heyderioquinone with sodium hydrosulfite) and found to be at least 0.68; which agrees with the value of 0.73 calculated on the basis of Sears' and Kitchen's work. This suggests that the less hindered hydroxyl is methylated and is indicative of structure I for heyderiol.[6]

The determination of the structure of heyderiol is important from the biochemical standpoint. It

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(3) E. A. Braude, *J. Chem. Soc.*, 490 (1945).

(4) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **22**, 1122 (1957).

(5) W. C. Sears and L. J. Kitchen, *J. Am. Chem. Soc.*, **71**, 4110 (1949).

(6) The ability of the demethylated hydroxyl to undergo stronger hydrogen bonding is also evident from the greater width of the OH absorption in case of hydroheyderioquinone as compared with heyderiol.[7]

(7) G. T. Bellamy, *The Infra-red Spectra of Complex Molecules*, London, Methuen & Co., Ltd., 1954, p. 92.

adds another member to the class of compounds with *p*-cymene carbon skeleton derived by oxidative coupling from the parent phenols, in the same way that lignanes are derived from the *n*-propylbenzene type phenols.

EXPERIMENTAL[8]

Isolation of heyderiol. The acetone extraction of a composite sample of sound incense cedar heartwood sawdust (8,640 g., dry wood basis) and the isolation of the libocedrol/*p*-methoxythymol complex from the petroleum ether soluble fraction of the extract was previously reported.[2] The mother liquors from the crystallization of the complex were evaporated to dryness, the residue steam distilled and the dark brown, semisolid nonvolatile portion recovered. It weighed 95 g. (1.1% dry wood basis).

A 23.5-g. portion of the material obtained was shaken with a mixture of 100 ml. of *n*-hexane and 100 ml. of 10% sodium hydroxide solution and filtered from an insoluble impurity. The aqueous phase was separated and the hexane solution extracted once more with 50 ml. of 10% sodium hydroxide. The aqueous phases were combined and extracted with 100 ml. of *n*-hexane in two portions. The combined organic extracts were dried with sodium sulfate, filtered, and evaporated to dryness to give 12.1 g. of a viscous, reddish liquid (0.57%).

This material was *p*-nitrobenzoylated in the usual way, using 15 g. of *p*-nitrobenzoyl chloride and 50 ml. of pyridine, then heating the resulting mixture for 1 hr. on a steam bath. To the cooled mixture, 500 ml. of 5% sodium carbonate solution was added and the whole extracted with 250 ml. of ethyl ether in three portions. The organic extracts were washed with 100 ml. of water, extracted with 500 ml. of 10% hydrochloric acid in two portions, dried with sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from acetone to give 8.5 g. of a pale yellow *p*-nitrobenzoate, m.p. 55–65° (unsharp). This ester was dissolved in 75 ml. of hot iso-octane, the solvent evaporated to about 25 ml. total volume to remove acetone of crystallization, the residue diluted with 50 ml. of iso-octane and the *p*-nitrobenzoate crystallized to give 6.55 g. of yellow crystals, m.p. 124–130°. Further purification was achieved by additional crystallizations from isooctane to give 4.38 g. of material, melting at 131–132° (0.14% yield, dry wood basis) and 1.65 g. of material melting at 128–155°, apparently consisting of a mixture of libocedrol and heyderiol *p*-nitrobenzoates.

An analytical sample of heyderiol *p*-nitrobenzoate was prepared by crystallization from iso-octane, m.p. 132.4–133.6°.

Anal. Calcd. for $C_{29}H_{33}NO_7$: C, 68.35; H, 6.92; N, 2.75; mol. wt 508. Found: C, 68.69; H, 6.76; N, 2.97; mol. weight (camphor) 480 ± 10%.

The *p*-nitrobenzoate of heyderiol represents a pale yellow, crystalline material when crystallized from acetone or acetone-alcohol mixtures, and intensive yellow crystals when crystallized from iso-octane or pure alcohol. The pale yellow form melts unsharply around 60° with some bubbles separating and probably contains acetone of crystallization. Upon standing, acetone is lost, the melting point becomes sharp, and rises to 124.4–124.7°. The *p*-nitrobenzoate in its intensive yellow form melts sharply and does not contain any solvent of crystallization. When treated with acetone it readily dissolves, but separates again in pale yellow form.

To obtain heyderiol from its ester, heyderiol/*p*-nitrobenzoate (2.987 g., m.p. 130–132°) was mixed with 10 ml. of ethanol to which 2 ml. of water and 1.0 g. of sodium hydroxide pellets was added. The resulting mixture was refluxed for 10 min., cooled, diluted to 30 ml. with cold water, and extracted with 40 ml. of chloroform in three portions. The extract was dried with sodium sulfate, filtered, and evaporated to dryness. The reaction product represented a viscous, oily liquid and weighed 2.1 g. (quantitative yield). After several months standing at room temperature, it solidified to a white, crystalline powder, m.p. 56–57°.

An analytical sample was prepared by crystallization from isooctane, m.p. 62.2–63.2°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3 17.32. Found: C, 73.68; H, 8.32; OCH_3, 17.66. Anal. for $C.CH_3$: Calcd. for $4CH_3$, 16.8, for $3CH_3$, 12.6. Found: 14.4.

Ultraviolet absorption spectrum: λ_{max} 287 mμ, log ϵ 3.92 (iso-octane).

Infrared absorption spectrum: μ_{max} 3520 cm.$^{-1}$ (free hydroxyl) (hexachlorobutadiene) ν_{max} 1595, 1620 (benzenoid) (KBr pellet).

In isooctane the free hydroxyl stretching absorption shifts to μ_{max} 3560 cm.$^{-1}$

Heyderioquinone. A 120-mg. portion of heyderiol, m.p. 53.5–55° was dissolved in 5 ml. of ethanol and refluxed with 350 mg. of ferric chloride hexahydrate for 30 min. The resulting solution was diluted to 15 ml. with water and extracted with 15 ml. of chloroform in two portions. The organic extract was dried over magnesium sulfate, filtered, and evaporated to dryness. Crystallization of the residue from methanol gave dark red needles, 77.3 mg., m.p. 122–123° (67% yield).

An analytical sample was prepared by repeated crystallizations from methanol, m.p. 124.0–124.4°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65; OCH_3, 9.06. Found: C, 73.55; H, 7.83; OCH_3, 9.34.

Ultraviolet absorption spectrum (methylcyclohexane): λ_{max} 235 mμ, log ϵ 4.15 (not very pronounced); 260 mμ, log ϵ 4.27 (quinoid A-band); infl. point at 284–285 mμ, log ϵ 3.57 (benzenoid B band); λ_{max} 363, log ϵ 2.98 (quinoid B band): 455 mμ, log ϵ 2.61; infl. point at 475 mμ, log ϵ 2.59 (quinoid C-band). Infrared absorption spectrum: ν_{max} 1660 cm.$^{-1}$ (conjugated carbonyl), 1615 cm.$^{-1}$ (conjugated double bond); also two bands at 1673 and 1640 cm.$^{-1}$ (KBr pellet). No OH band (carbon tetrachloride).

Nuclear magnetic resonance spectrum: (40-mc. frequency; carbon disulfide as a solvent; shifts in reference to ethanol hydroxyl band). A triplet with maxima at −1.45, −1.30, and −1.15 parts per million (rel. intensity 1.0: 1.0:1.1 units); a singlet at +1.3 parts per million (rel. intensity 3.0 units); a doublet with maxima at +2.70 and +3.00 parts per million (rel. intensity 3.0:3.1 units); and a doublet with maxima at +3.80 and +3.95 parts per million (rel. intensity 6.0:6.0 units).

Hydroheyderioquinone. A 501-mg. portion of heyderioquinone, m.p. 122–123°, was dissolved in 25 ml. of *n*-hexane to which a few ml. of chloroform was added to increase the solubility. The resulting liquid was shaken with a solution of 5.0 g. of sodium hydrosulfite in 25 ml. of water. The organic layer became gradually colorless; it was separated and the aqueous portion extracted with 15 ml. of chloroform. The organic extracts were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 10 ml. of *n*-hexane and allowed to crystallize at −5° to give 454 mg. of a white, crystalline material, m.p. 89–90° (90% yield).

An analytical sample was prepared by crystallizations from *n*-hexane, m.p. 91.2–92.4°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.20. Found: C, 73.19; H, 8.12.

Ultraviolet absorption spectrum (iso-octane): λ_{max} 288 mμ, log ϵ 3.93. Infrared absorption spectrum: ν_{max} 3520 and 3580 cm.$^{-1}$ (free OH stretching of the two hydroxyls) (carbon tetrachloride). In iso-octane the above maxima

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(8) All melting points are corrected. Microanalysis by Microchemical Laboratory, University of California, Berkeley. Ultraviolet and infrared spectra were obtained on Beckman DK II and Perkin-Elmer Model 21 recording spectrophotometers, respectively, and the NMR spectra on Varian Associates high resolution NMR spectrometer.

shift to 3560 and 3600 cm.$^{-1}$, respectively. No carbonyl band (KBr pellet).

Oxidation of heyderioquinone. A 142-mg. portion of heyderioquinone, m.p. 122–123° was dissolved in 5 ml. of acetone to which 0.5 ml. of 30% hydrogen peroxide was added. The resulting mixture was heated to 50°, treated with 0.5 ml. of 10% sodium carbonate solution, and refluxed for 3 min. when it became yellow. One half ml. of 25% sodium solution was then added to the liquid which was refluxed for 5 min. when it became brown-red. Upon acidification with 15 ml. of 10% sulfuric acid the material was extracted with 30 ml. of n-hexane in two portions, the solvent evaporated, and the residue heated for 10 min. on a steam bath with 10 ml. of 10% sulfuric acid. The resulting liquid was cooled, diluted with 20 ml. of water, and extracted with 25 ml. of n-hexane in two portions. The combined n-hexane extracts were, in turn, extracted with 45 ml. of 10% sodium hydroxide solution in three portions, the aqueous solutions acidified with concentrated hydrochloric acid, and extracted with 25 ml. of chloroform in three portions. The chloroform solutions were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from 3 ml. of n-hexane to give 39 mg. of p-methoxycarvacrol, m.p. 64–65° (52% yield).

Further purification was achieved through sublimation at 100° and 2-mm. pressure to give material melting at 66.2–66.6°. The melting point remained undepressed on admixture of the authentic sample. The infrared spectrum (KBr pellet technique) of the p-methoxycarvacrol isolated in this experiment was found to be identical to the one of an authentic sample.[9]

Norheyderioquinone. A 106 mg. portion of heyderiol, m.p. 53.5–55° was dissolved in a mixture of 6 ml. of acetic and 4 ml. of hydriodic acids, containing a few crystals of stannous chloride. The resulting liquid was refluxed for 135 min., cooled, diluted with 25 ml. of water, and extracted with 15 ml. of chloroform in two portions. The chloroform extracts were diluted with 10 ml. of acetone and treated with 1.0 g. of ferric chloride hexahydrate for 3 min. Upon addition of 25 ml. of water, the chloroform layer was separated and the aqueous phase washed with 10 ml. of chloroform. The organic extracts were combined, dried with magnesium sulfate, filtered, and evaporated to dryness. The residue was crystallized from methanol-water mixture to give 76 mg. of a dark brown crystalline powder, m.p. 120–121° (78% yield).

An analytical sample was prepared by crystallizations from methanol-water mixtures, m.p. 123.6–124.4°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.09; H, 7.14.

Ultraviolet absorption spectrum (iso-octane): infl. point at 235 mμ, log ϵ 4.10 (not very pronounced); λ_{max} 259 mμ, log ϵ 4.33 (quinoid A band); 284–285 mμ, log ϵ 3.65 (benzenoid B band); 368 mμ, log ϵ 3.01 (quinoid B band); 450 mμ, log ϵ 2.66 and infl. point at 470 mμ, log ϵ 2.63 (quinoid C band). Infrared absorption spectrum: ν_{max} 3340 cm.$^{-1}$ (Nujol) (OH stretching); 1658 cm.$^{-1}$ (conjugated carbonyl); 1615 (conjugated double bond band); two additional bands at 1670 and 1635 (KBr pellet).

Pyrolysis of norheyderioquinone. A 69 mg. portion of norheyderioquinone, m.p. 120–121°, was heated in a Pyrex test tube for 60 min. at 210–220°. During heating a yellow colored sublimate appeared on the walls of the cold part of the vessel. The test tube was cooled, the total pyrolysis product dissolved in 25 ml. of ethyl ether, and extracted with 50 ml. of 10% sodium carbonate solution in three portions. The aqueous extracts appeared violet in color. The color changed to yellow upon acidification with 10% hydrochloric acid and a yellow precipitate appeared. The aqueous mixture was extracted with 25 ml. of chloroform in three portions, the organic extracts dried over sodium sulfate, filtered, evaporated to dryness, and the residue sublimed at 100° and 23-mm. pressure to give 4.5 mg. of 3-hydroxythymoquinone (12% yield), m.p. 160–161° (sealed capillary). Further purification by repeated sublimation raised the melting point of the compound to 166.0–166.5° (sealed capillary), undepressed on admixture with an authentic sample. The infrared spectra of the reaction product and of an authentic sample of 3-hydroxythymoquinone were found to be identical (KBr pellet technique).

Synthesis of heyderiol. To a solution of 3.1 g. of p-methoxythymol, n_D^{23} 1.5253, and 2.0 g. of p-methoxycarvacrol, m.p. 64–65°, in 125 ml. of carbon tetrachloride there was added a solution of 20 g. of sodium hydroxide in 125 ml. of water. To this vigorously stirred liquid a solution of 9.4 g. of potassium ferricyanide in 100 ml. of water was added dropwise during a 1 hr. period. The yellowish reaction mixture was acidified with concentrated hydrochloric acid and the separated aqueous phase extracted with 30 ml. of chloroform. The organic extracts were combined and evaporated to dryness. The residue was dissolved in 50 ml. of n hexane, dried with sodium sulfate, filtered, evaporated to 10 ml., mixed with 1.5 g. of p methoxythymol, diluted to 30 ml. with n-hexane, and crystallized to −5°. The collected crystalline precipitate was washed with n-hexane to give 1.131 g. of libocedrol/p-methoxythymol addition complex, m.p. 88.5–90°.

The filtrate from the crystallization was reduced to 20 ml. and extracted with 100 ml. of 10% sodium hydroxide solution in four portions. The aqueous extracts were acidified, extracted with 50 ml. of chloroform in two portions, dried with sodium sulfate, filtered, evaporated to dryness and the residue distilled at 40-mm. pressure to give 2.2 g. of p-methoxythymol, containing possibly some p-methoxycarvacrol, n_D^{22} 1.5283, b.p. 160–165°.

The extracted n-hexane solution was dried with sodium sulfate, filtered, and evaporated to dryness to give 2.5 g. of a viscous residue. The latter was p-nitrobenzoylated in the usual way, using 3.0 g. of p-nitrobenzoyl chloride, 10 ml. of pyridine, and heating the resulting mixture for 1 hr. on a steam bath. The reaction mixture was cooled, treated with 75 ml. of 3% sodium carbonate solution and extracted with 60 ml. of ethyl ether. The ethyl ether solution was extracted with 50 ml. of 10% sodium carbonate solution, washed with 100 ml. of water, extracted with 100 ml. of 10% hydrochloric acid, washed with 100 ml. of water again, dried with sodium sulfate, filtered, and evaporated to dryness.

The residue was crystallized from 15 ml. of acetone to give 410 mg. of a yellow substance, m.p. 55–75°. The material obtained was dissolved in 30 ml. of hot iso-octane and the solvent evaporated to remove acetone of crystallization. The residue was crystallized from 25 ml. of iso-octane to give 326 mg. of yellow crystals, m.p. 129–133° (6% yield). Further purification by crystallization from acetone and from iso-octane raised the melting point to 132.6–133.2°. Heyderiol was prepared from its p-nitrobenzoate through alkaline hydrolysis and crystallization from iso-octane, as described, m.p. 61.2–62.2°. Heyderioquinone was prepared from heyderiol through oxidation with ferric chloride, as described, m.p. 123.2–123.7°. The melting points of the three materials was undepressed on admixture with the corresponding natural compounds, and the infrared spectra of any pair were found to be identical (KBr pellet technique).

Determination of the hydrogen bonding indices. Fig. 2 depicts the infrared spectra of heyderiol and hydroheyderioquinone in the region between 3000 and 4000 cm.$^{-1}$ at various concentrations and in the melt form. Assuming ν_{max} of 3460 cm.$^{-1}$ for the band corresponding to the hydroxyl group of heyderiol, engaged in hydrogen bonding and ν_{max} 3560 cm.$^{-1}$ for the free hydroxyl band (iso-octane solution), the calculation gives 0.30 for the corresponding hydrogen bonding index. In case of hydroheyderioquinone two bands corresponding to the free hydroxyl vibration are present at ν_{max} 3560 and 3600 (iso-octane solution). The

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(9) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 20, 443 (1955).

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.

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]

Acknowledgments. We are indebted to Mrs. Rosalind M. Smith for determining the ultraviolet and infrared spectra, to Dr. P. Sogo and his coworkers for determining the NMR spectra, to the California Cedar Products Co. for sponsoring a research grant supporting this investigation and to Mr. Charles P. Berolzheimer for his interest and cooperation.

RICHMOND, CALIF.

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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).

[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

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

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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 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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[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).

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