

Studies on Conidendrin*

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Hypobromite oxidation of α -conidendrin dimethyl ether gives among other products a neutral substance which is shown to be 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthaldehyde. β -Conidendrin dimethyl ether is very stable to hypobromite. The diol corresponding to β -conidendrin dimethyl ether has been prepared.

During his studies on "sulphite-liquors lactone", conidendrin (I), Holmberg¹ oxidised α -conidendrin dimethyl ether with hypobromite and obtained two acids later identified by Erdtman² as 6-veratroylveratric acid (II) and 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-1,2,3,4-tetrahydro-2,3-naphthalene-dicarboxylic acid (III), and in addition a neutral compound $C_{16}H_{10}O(OCH_3)_4$ which according to Erdtman was probably a carbonyl compound. The structure of this product was never elucidated.

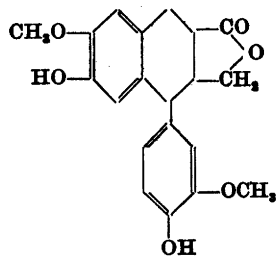
Conidendrin, formerly a substance of purely academic interest is now available in very large quantities due to the observation that the waste liquor from sulphite pulping of *Tsuga heterophylla*, "Western hemlock", contains unusually large amounts of conidendrin, and the excellent work done by the chemists of The Crown Zellerbach Company, Camas, which resulted in a convenient method of isolating conidendrin from this material³. Conidendrin is therefore now a potential technical raw material and one suggested utilisation is the production of the nor-conidendrin compounds possessing good anti-oxidising properties⁴⁻⁷.

Attempts have been made to increase the yield of the dicarboxylic acid (III) which appeared to be an interesting intermediate for various synthetic products, by varying the procedure employed by Holmberg, *e. g.* by using hypochlorite or hypoiodite instead of hypobromite. Oxidation with permanganate was also attempted: under no conditions was the yield increased, but a reasonable amount of Holmberg's neutral compound was obtained and the structure of this substance has now been determined. The correct composition

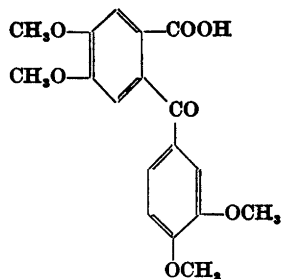
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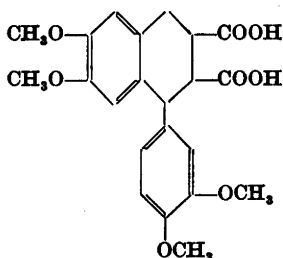
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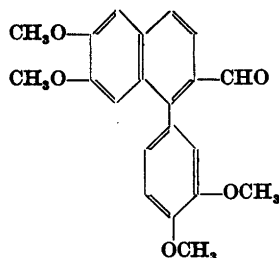
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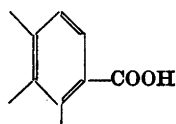
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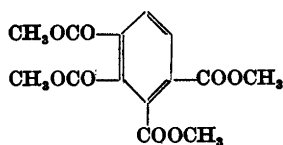
III



IV



V



VI

was found to be $C_{17}H_8O(OCH_3)_4$ and the substance yielded a 2,4-dinitrophenylhydrazone and an oxime. The latter could be dehydrated by acetic anhydride to a nitrile, which was hydrolysed to the corresponding carboxylic acid. The substance, consequently, must be an aldehyde. Direct oxidation of this very sparingly soluble aldehyde to the carboxylic acid with permanganate under various conditions was at first unsuccessful, the compound being recovered unchanged or being completely destroyed. Ultimately it was found that the acid could be obtained by oxidation in pyridine solution.

In order to locate the carboxyl group in this acid, which from its composition appeared to be a phenyl naphthalene carboxylic acid, it was demethylated and the crude reaction product oxidised with permanganate. An acid was obtained, which was methylated with diazomethane, and the resulting ester was found to be identical with prehnitic acid tetramethyl ester (VI) prepared as described by Smith and Carlson⁸. The ester exhibited the peculiar purple coloration on exposure to light described by these authors. The colour was

quite distinct after 10—15 minutes' irradiation with ultraviolet light and disappeared on melting or recrystallisation.

The isolation of prehnitic acid proves conclusively that the structure of the acid is 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthoic acid (V). This acid was also found to be identical with a synthetic sample recently prepared by Walker⁹ and kindly furnished by him. The corresponding aldehyde, Holmberg's "neutral substance", is consequently 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthaldehyde (IV). Holmberg reported a yield of about 6% but this may be increased by slight modification of the original method. Holmberg mixed a solution of α -conidendrin dimethylether in alkali with a hypobromide solution and heated the mixture on a boiling water-bath. If, however, the solutions are heated almost to the boiling point prior to the mixing a 10—12% yield is obtained.

If, instead of α -conidendrin dimethyl ether, the β -isomer was oxidised with hypobromite no aldehyde or only traces of the aldehyde (IV) and a little 6-veratroylveratric acid were obtained, the bulk of β -lactone being recovered unchanged. When the phenyltetralin-dicarboxylic acid (III) was subjected to hypobromite oxidation it was also largely recovered unchanged and only traces of 6-veratroylveratric acid could be isolated. Thus it is obvious that the oxidation of α -conidendrin dimethyl ether (or rather the corresponding hydroxy acid) follows three distinctly different routes; the first leading to the aldehyde (IV), the second to the dicarboxylic acid (III) and the third to 6-veratroylveratric acid but there may, of course, be a common primary reaction stage.

Haworth and Wilson¹⁰ have reduced α -conidendrin dimethyl ether with lithium aluminium hydride and obtained a diol m. p. 167—168° identical with (+) *iso*-lariciresinol dimethyl ether. The same diol has now been obtained from the dimethylester of Holmberg's phenyltetraline dicarboxylic acid (III). Hence this acid retains the configuration of the α -conidendrin series and it is obviously formed by direct oxidation of the $-\text{CH}_2\text{OH}$ group to $-\text{COOH}$. As expected β -conidendrin dimethylether on reduction with lithium aluminium hydride furnished a different diol (m. p. 140—142°).

EXPERIMENTAL *

Composition of Holmberg's "neutral substance". The aldehyde (IV) was purified by distillation *in vacuo* and by several crystallizations from glacial acetic acid and ethanol. M. p. 182—183°. (Found: C 71.84, 71.13; H 6.18, 5.91; OCH_3 35.6. Calc. for $\text{C}_{21}\text{H}_{20}\text{O}_5$ (352.4): C 71.58; H 5.72; OCH_3 35.23).

6,7-Dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthaldehyde-2,4-dinitrophenylhydrazone. Hot solutions of the aldehyde (IV) (0.5 g) and of 2,4-dinitrophenylhydrazine (0.7 g) in glacial acetic acid were mixed and heated on a water-bath for 15 minutes. The red precipitate was collected while hot and crystallized from glacial acetic acid. M. p. 289—291° (decomp.). (Found: OCH_3 22.9). Calc. for $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_8$ (532.5): OCH_3 23.3.

6,7-Dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthaldehyde oxime. A solution of the aldehyde (IV) (1 g) and of hydroxylaminehydrochloride (1 g) in absolute ethanol (50 ml) and pyridine (4 ml) was boiled under reflux for two hours. The solution was evaporated to dryness and the residue washed with water. The product (1 g) was crystallized from ethanol. M. p. 185—186°. (Found: N 3.68). Calc. for $\text{C}_{21}\text{H}_{21}\text{NO}_5$ (367.4): N 3.81.

* All melting points uncorrected.

6,7-Dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthoic acid nitrile. A solution of the oxime above (0.7 g) in acetic anhydride (20 ml) was heated under reflux for 1.5 hours. Water (50 ml) was added carefully and the mixture heated on a water-bath for half an hour and then poured into a large volume of water (450 ml). On cooling a slightly yellow precipitate was formed. Crystallization from ethanol (animal charcoal) gave a colourless product. M.p. 185–186° depressed on mixing with the starting material to 165–170°. (Found: C 72.46; H 5.42; N 3.92; OCH₃ 35.77. Calc. for C₂₁H₁₉NO₄ (349.4): C 72.19; H 5.48; N 4.01; OCH₃ 35.53).

6,7-Dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthoic acid. Method A: The nitrile above was boiled with ethanolic potassium hydroxide (ethanol 20 ml, potassium hydroxide 8 g) for three days. Some ammonia was still being evolved but the mixture was cooled and acidified with conc. hydrochloric acid (10 ml). The heavy precipitate (containing hydrated silica from the glass vessel) was extracted with boiling ethanol and the combined extracts precipitated with water. The product was dissolved in dilute sodium hydroxide separated from some undissolved material, acidified with dilute hydrochloric acid and the precipitate crystallized from ethanol. M. p. 202–203°.

Method B: A mixture of the aldehyde (IV) (3 g), dissolved in pyridine (60 ml) containing a little sodium hydroxide (2 ml) (2 N), and potassium permanganate (1.1 g) in water (60 ml) was heated on a water-bath for half an hour with occasional shaking, cooled and acidified with a mixture of conc. sulfuric acid (50 ml) and water (150 ml). Sodium bisulphite was added to dissolve the manganese sludge and the remaining product was dissolved in dilute sodium hydroxide and precipitated with acid yielding the acid (V) (2.8 g), m. p. 202–203° after crystallization from ethanol. The m. p. was undepressed when the compound was mixed with the acid from the nitrile. (Found: C 68.8; H 5.7; OCH₃ 33.8; Eqv. weight 376. Calc. for C₂₁H₂₀O₆ (368.4): C 68.47; H 5.47; OCH₃ 33.7; Eqv. weight 368).

Methyl ester of the above acid. The acid (V) was dissolved in methanol and treated with an excess of diazomethane in ether. The solvent was evaporated and the residual ester crystallized from methanol. M. p. 151.5–152.5°. (Found: OCH₃ 40.33. Calc. for C₂₂H₂₂O₆ (382.4): OCH₃ 40.58).

Oxidation of 6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)-2-naphthoic acid (V) to 1,2,3,4-benzenetetracarboxylic acid. The acid (V) (1 g) was heated with pyridine hydrochloride (5 g) at 180° for 2 hours. The mixture was then poured into dilute hydrochloric acid (200 ml) and continuously extracted with ether for 12 hours. On evaporation of the ether layer a light brown product (0.8 g) was obtained. This was immediately dissolved in water (100 ml) containing potassium hydroxide (0.1 g) and finely ground potassium permanganate (9 g) was added. The mixture was heated on a water-bath for 2 hours with mechanical stirring. Excess permanganate was destroyed with ethanol and the solution filtered. The filtrate, acidified with hydrochloric acid, was passed through a cation exchanger (IR 120) which was then washed with hydrochloric acid (4 N) and the eluate evaporated to dryness when a solid product (0.4 g) was obtained.

Crystallization from hydrochloric acid (1 : 1) gave a product m. p. 215–225° (decomp.). (Found: Eqv. weight 64.5. Calc. for C₁₀H₆O₈ (254): Eqv. weight 63.5).

The substance was dissolved in methanol and treated with an excess of diazomethane in ether. The ester was obtained in almost quantitative yield. M. p. from methanol 126–126.5° undepressed when the compound was mixed with an authentic specimen of tetramethyl-1,2,3,4-benzenetetracarboxylate.

is o-Lariciresinol dimethylether. The dimethylester of the phenyltetralindicarboxylic acid (III)² (0.5 g) was reduced with lithium aluminium hydride (0.5 g) following the procedure of Haworth and Wilson⁶. The product was crystallized from methanol. M. p. 175.5–176.5° and 172–175° when mixed with the diol (m. p. 171–172°) below, [α]_D²⁰ +23° (c 1.172 in chloroform).

For comparison *a*-conidendrin dimethylether was also reduced and the product crystallized from methanol. M. p. 171–172°, [α]_D²⁰ +21° (c 1.930 in chloroform) or +29° (c 2.552 in acetone). Haworth and Wilson give m. p. 167–168°, [α]_D²⁰ +18° in chloroform.

Diol from β-conidendrin dimethyl ether. A slight modification of the method above was used when the β-conidendrin dimethyl ether was reduced. After decomposing the metal alkoxide it was necessary to extract with hot benzene to get the organic material in solution. The crude product melted at 126–129°. After crystallization from benzene it

melted at 82–84°, solidified if the melt was held at 105–110° for some time, shrank from 132°, and there were some signs of a new solidification before it melted at 140–142°. $[\alpha]_D^{20} + 46.2^\circ$ (*c* 2.33 in chloroform). (Found: C 67.56; H 7.56; OCH₃ 32.36. Calc. for C₂₃H₂₈O₆ (388.4): C 68.02; H 7.26; OCH₃ 31.95.)

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