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A Synthesis of Confiferyl Alcohol¹ and Confiferyl Benzoate

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In 1874, Tiemann² hydrolyzed the glucoside, coniferin, by means of emulsin, into an alcohol and glucose. The new substance was named confiferyl alcohol. Its structure (I) was shown to be that of 3-methoxy-4-hydroxycinnamyl alcohol by process of degradation.³ Among these reactions were oxidative cleavage, which gave vanillin and acetaldehyde, and alkaline fusion that yielded protocatechuic and acetic acids. This evidence served to locate the double bond in the side chain. It was also observed that confiferyl alcohol very readily undergoes polymerization.

We have achieved a synthesis of confiferyl alcohol, making use of the recently announced reagent, lithium aluminum hydride.⁴ The ester group of ethyl acetoferulate (II) is selectively reduced by this reagent, and the acetyl group is removed during the process. The reaction proceeds stepwise; a salt-like substance containing both lithium and aluminum separates first. Upon treatment with aqueous ammonium carbonate or sulfate, or boric acid, this "salt" gives confiferyl alcohol.

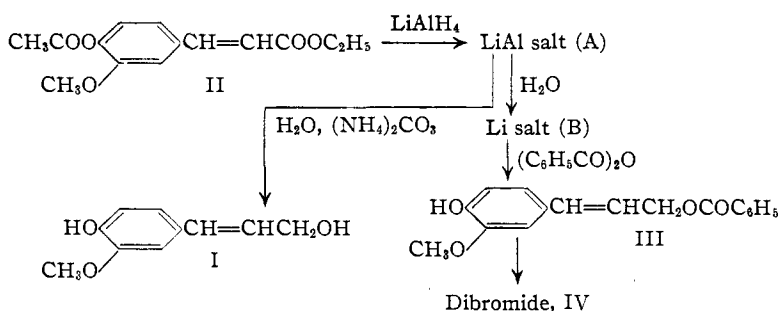
This selective reduction was unexpected since it had been stated that cinnamic acid was completely reduced by lithium aluminum hydride to γ -phenylpropyl alcohol.⁵ Subsequently, however,⁶ it was found that cinnamic aldehyde could be selectively reduced by this reagent to cinnamyl alcohol at -10° .

The properties of the synthetic confiferyl alcohol resemble those recorded by Tiemann. It melted at $72-73^{\circ}$, corrected (Tiemann gave $73-74^{\circ}$), showed the correct analysis and molecular weight, gave protocatechuic acid upon alkaline fusion, was easily converted to the characteristic yellow ammonium and lead salts,⁷ formed polymeric material with exceeding ease, and in particular, showed a great reluctance to crystallize, even when seeded.

Dr. A. L. Geddes, of these Laboratories, determined the infrared absorption spectra of this confiferyl alcohol; the characteristic region, $5.5-10.5\mu$, is shown in Fig. 1. The infrared curve of isoegenol is shown for comparison, the similarity

of the curves being indicative of like structures. The band near 10.35μ is evidence in favor of the structure $RCH=CHR'$, but the other ethylenic band near 6.05μ is weak, being entirely missing in isoegenol. For this reason, isoegenol dibromide was made to be sure the specimen was really unsaturated in the side chain.

Confiferyl benzoate (III) was obtained in the following manner: The "salt" containing lithium and aluminum was treated with water, which



removed the aluminum, leaving lithium coniferate. The latter was fused with benzoic anhydride to give the known confiferyl monobenzoate (III).⁸ The melting points of the ester and of its dibromide agree with those recorded in the literature, and corroborate the alcohol synthesis. The benzoate is the major constituent of Siamese gum benzoin.⁸ Confiferyl alcohol has been obtained previously only by fermentation processes.^{2,9}

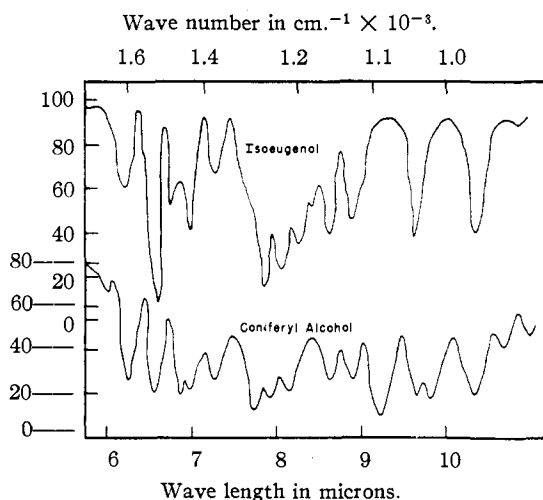


Fig. 1.

(1) A preliminary announcement of this work appeared in *Science*, **107**, 269 (1948).

(2) Tiemann and Haarman, *Ber.*, **7**, 608 (1874).

(3) Tiemann, *ibid.*, **11**, 659 (1878).

(4) Finholt, Bond and Schlesinger, *THIS JOURNAL*, **69**, 1199 (1947).

(5) Nystrom and Brown, *ibid.*, **69**, 2549 (1947).

(6) Hochstein and Brown, *ibid.*, **70**, 3485 (1948).

(7) Tiemann, *Ber.*, **8**, 1132 (1875).

(8) Zinke and Dzirmal, *Monatsh.*, **41**, 423 (1920).

(9) Pauly and Feuerstein, *Ber.*, **62**, 305 (1929).

Experimental

Acetylferulic acid¹⁰ gave an 82% yield of the acid chloride when refluxed for half an hour with thionyl chloride. A mixture of the acid chloride and absolute ethanol gave a 70% yield of the ethyl ester (II), m.p. 120–121°, b.p. 186–189 (5 mm.), on refluxing and distilling.

Anal. Calcd. for C₁₄H₁₆O₅: C, 63.6; H, 6.1; mol. wt., 264. Found: C, 62.9; H, 5.9; mol. wt., 250.

Coniferyl Alcohol (I).—All operations were carried out in an atmosphere of dry, oxygen-free nitrogen. The ether was dried over calcium hydride. A typical run follows: In a 2-l. three-necked flask, fitted with a reflux condenser protected by a drying tube, a low-temperature thermometer, dropping funnel, and a stirrer, there was placed a solution of 2.5 g. (0.0658 mole) of lithium aluminum hydride in 400 ml. of dry ether. The flask was immersed in an ice-salt-bath and cooled until the contents were at –15°. Over a period of two hours, a solution of 9 g. (0.034 mole) of ethyl acetoferulate in 700 ml. of ether was added dropwise, care being taken that the temperature never exceeded –10°. Stirring was continued for two hours after the addition had been completed, and the mixture was then allowed to stand overnight, and come to room temperature. The pale yellow solid was then collected on a filter, and rinsed twice with 100-ml. portions of dry ether to remove any unchanged ester and reagent. The amount of solid (salt B) was 9.8 g.

The yellow solid was added, in portions, with shaking between additions to a solution of 5 g. of ammonium carbonate (monohydrate) in 250 ml. of water, overlaid by 100 ml. of ordinary ether. The ether layer was separated, and the aqueous solution extracted with two 100-ml. portions of ether. The combined ethereal solutions were concentrated to a volume of 50 ml., and 750 ml. of dry petroleum ether (b.p. 35–55°) added, with shaking. The cloudy solution was then placed in an ice chest for several days, until crystallization appeared to be complete. The coniferyl alcohol was then filtered and rinsed with 10 ml. of dry petroleum ether. The yield was 2.6 g. (42.6%); m.p. 72–73°.

As noted by Tiemann, coniferyl alcohol shows a great reluctance to crystallize. A minimum of three days in the ice-chest was required, even with scratching and seeding; sometimes eight days elapsed before any solid separated. Recrystallizations were just as unsatisfactory.

When the procedure was modified by evaporating the ether and distilling the residue *in vacuo*, an apparent yield of 5 g. (73.7%), b.p. 163–165° (3 mm.), was obtained, but on crystallization the solid recovered was the same as that given above. The melting point was not raised above 72–73° by recrystallizations.

Anal. Calcd. for C₁₀H₁₂O₂: C, 66.6; H, 6.7; mol. wt., 180. Found: C, 66.0; H, 6.5; mol. wt. (in C₆H₆), 173.

Coniferyl alcohol slowly decomposes on standing.

The specimen of coniferyl alcohol so prepared formed the characteristic yellow ammonium salt, as described by Tiemann. This salt sometimes separated if the decomposition

of the lithium salt was carried out by using ammonium sulfate (10.5 g. in 20 ml. of water).

Coniferyl Benzoate (III).—When the solid from the reaction mixture was decomposed by the addition of 20 ml. of water only, it turned a bright yellow; this yellow salt was removed by filtration, rinsed with alcohol, and dried.

The dry salt was mixed with a 50% excess of benzoic anhydride and warmed on the steam-bath for one-half hour. The melt was then steam distilled to remove the benzoic acid. When the residual solution was cooled, the coniferyl benzoate crystallized from ether or aqueous methanol. The yield was 9 g. (67.3%) and the melting point was 70–71° (Zinke and Dzimal give 72°).⁸

Attempts to hydrolyze the benzoate to coniferyl alcohol were unsuccessful, the polymeric product being obtained in all instances, even with dilute ammonia.

The dibromide⁸ was prepared by dissolving 2 g. of coniferyl benzoate in 75 ml. of carbon disulfide, and adding, dropwise, 1.23 g. of bromine in 15 ml. of the same solvent. The bromine color disappeared instantly. The resultant reddish solution was permitted to evaporate spontaneously, and the residue recrystallized several times from a mixture of ether and petroleum ether. The yield was 2 g., m.p. 114–116°. It dissolves in concentrated sulfuric acid to give a yellow solution, which turns blue when heated gently.

Protocatechuic acid was obtained by alkaline fusion of coniferyl alcohol, using the procedure recently described by Pearl.¹¹ One gram of alcohol gave 0.5 g. of protocatechuic acid, which, after crystallization from benzene, formed fine white needles, m.p. 199–200°. A mixed melting point with an authentic specimen was not depressed.

Isoeugenol dibromide was formed in a nearly quantitative yield by bromination in carbon tetrachloride solution; the bromine color disappeared instantly as each drop of reagent was added. After recrystallization from ligroin (b.p. 90–120°), the melting point was 95–96°. The value is recorded in the literature as 94–95°.¹²

Summary

The syntheses of two naturally occurring substances, coniferyl alcohol and coniferyl benzoate, are described.

Coniferyl alcohol, 3-methoxy-4-hydroxycinnamyl alcohol, has been obtained by the reducing action of lithium aluminum hydride on ethyl acetoferulate.

Coniferyl benzoate was prepared by treating the intermediate lithium coniferate with benzoic anhydride.

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(11) Pearl, *ibid.*, **68**, 2181 (1946).

(12) Auwers and Müller, *Ber.*, **35**, 121 (1902).

(10) Fosdick and Starke, *THIS JOURNAL*, **62**, 3353 (1940).