ISOLATION, CHARACTERIZATION AND SYNTHESIS OF 3-METHOXY-4,5-METHYLENEDIOXYCINNAMALDEHYDE: A NOVEL CONSTITUENT FROM *CANELLA WINTERANA*

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ABSTRACT.—An alcoholic extract of *Canella winterana* yielded, upon further purification, an α,β-unsaturated aldehyde which was characterized as 3-methoxy-4,5-methylenedioxycinnamaldehyde (1). The identity of this compound was established by investigation of its spectral features, by chemical derivatization to alcohols 3 and 4, and by chemical synthesis from 5-hydroxyvanillin.

The trunk bark of *Canella winterana* has often been used as a flavoring agent because of its spicy constituents, such as eugenol and cineol (1). Recently, it was found (2) that one of its constituents was the pungent sesquiterpene dialdehyde canellal (2), which was reported to have strong antifungal and insect antifeedant activities. As a part of a research program exploring the chemistry and biology of canellal (2), several collections of the trunk bark were processed for its isolation to have it available in ample amounts. One of such collections was found to contain only a trace of the desired material, but it yielded a new crystalline compound whose isolation, identification, and synthesis are the subject of this paper.

Alcohol extraction of the trunk bark of *Canella winterana* (Canellaceae) followed by solvent partitioning and column chromatography (see Experimental) provided a yellow crystalline substance, $C_{11}H_{10}O_4$, mp 136–137°, which was optically inactive. The ir spectrum (CHCl$_3$) indicated that the compound was aromatic (1600 cm^{-1}) and contained an α,β-unsaturated carbonyl function (1630 and 1675 cm^{-1}). The pmr spectrum (CDCl$_3$) was in agreement with the above findings as it exhibited a one-proton doublet at $\delta 9.66$ ($J = 7.8$ Hz) which could be attributed to an aldehyde function in conjugation with a double bond. The two protons of the conjugated double bond formed an AB system, of which the A portion was further split by the aldehyde proton giving rise to a pair of doublets at $\delta 6.37$ and $\delta 6.64$ (J = 7.8 and 16.2 Hz). The B portion, on the other hand, appeared as a doublet at $\delta 7.31$ ($J = 16.2$ Hz). This latter large coupling constant suggested an *E*-configuration. The pmr also showed a three-proton singlet at $\delta 3.93$ which was ascribed to a methoxy group and a two-proton singlet at $\delta 6.02$ suggesting a methylenedioxy group. The two remaining aromatic hydrogens absorbed as another two-proton singlet at $\delta 6.73$; this made it possible to conclude that structure I is the one most likely to account for this accidental magnetic equivalence. All other possible structural isomers were unlikely to give two magnetically equivalent aromatic protons.

The ^{13}C nmr spectrum (CDCl$_3$) was in agreement with the information obtained so far as it exhibited an aldehydic carbonyl (doublet in the off-resonance spectrum) at $\delta 193.0$, three singlets due to C–3, C–4 and C–5 at $\delta 149.8$, $\delta 138.5$ and $\delta 144.0$, respectively; the other singlet in the spectrum, at $\delta 129.1$, was due to C–1. The spectrum also exhibited four additional doublets at $\delta 152.2$, $\delta 127.5$, $\delta 110.3$ and $\delta 101.9$. The first two (3) were due to the β and α carbons, respectively, while the outer two signals must be due to C–2 and C–6. The remaining signals in the

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[1]An undergraduate research participant, NSF, 1979.

spectrum were a quartet at δ56.9 due to the methoxy carbon and a triplet at δ102.2 and were ascribed to the methylenedioxy carbon.

Borohydride reduction of **1** using an ion exchange resin in the borohydride form[2, 3] proceeded smoothly to yield the allylic alcohol **3**, mp 83–84°, and with spectral data in agreement with the expected structure. Catalytic hydrogenation of **3** gave a quantitative yield of the dihydroderivative **4**.

1, R=-CHO
3, R=-CH₂OH
5, R=-COOH

2
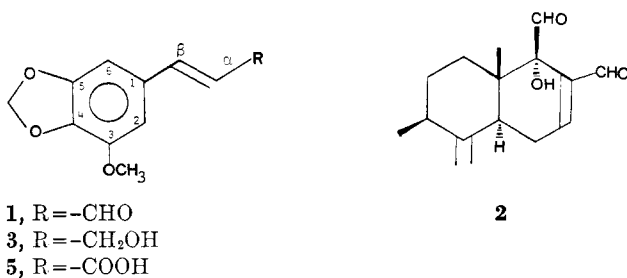
In order to confirm structure **1**, it was first thought that the best approach was to oxidize it to the analogous acid **5** which had been previously reported (4). This direction was abandoned when it was discovered that unfortunately the literature contained no spectral data about **5**, and even its melting point was ambiguously reported as 222–226° (dec.) in one paper (4) and 200° (sintering) and 228° (dec.) in another (4). Therefore, it was decided to confirm the structure of the isolated material by synthesis. Another reason for developing a practical synthetic route to this compound was the apparent growing interest in the study of the biological properties of α,β-unsaturated aromatic aldehydes due to their reported carcinogenicity, especially among furniture workers (5). A straightforward synthetic scheme would be of value in making this compound available in sufficient amounts for biological evaluations.

6   **4**
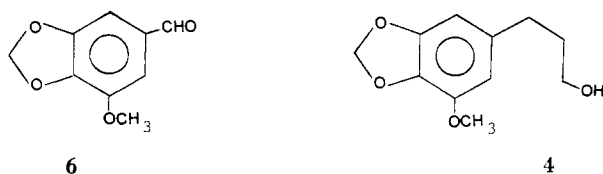
The starting material for this synthesis was 5-hydroxyvanillin, which is commercially available,[3] and can be prepared from 5-iodovanillin (6). Methylenation of 5-hydroxyvanillin was achieved by treatment with methylene bromide in the presence of sodium hydroxide and a phase transfer catalyst.[4] This modified procedure provided myristicin aldehyde (**6**) more conveniently and in a better yield than the described procedure described in the literature (7). The product was then converted to the acid **5**, as previously described (4). It was then reduced to the aldehyde **1** by conversion, first, to the acid chloride (not isolated) with the use of thionyl chloride in the presence of dimethylformamide then reduction

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[2]We have found that reductions with this reagent proceed cleanly to the allylic alcohol without hydrogenation of the double bonds. The reaction is, however, slower than with sodium borohydride.

[3]Obtained from Tridom Chemical Inc.

[4]Adogen 464, available from Aldrich Chemical Co.

with bis(triphenylphosphine)tetrahydroborate copper I (8).[5] The product was indistinguishable from the natural material. It should be noted that an attempt to use lithium tritertiarybutyl aluminum hydride to reduce the acid chloride to **1** was unsuccessful. A catalytic Rosenmond-type reduction was not attempted to avoid reduction of the olefinic double bond. Reduction with the copper-triphenylphosphine reagent, on the other hand, proceeded smoothly and yielded the desired aldehyde as the sole product.

EXPERIMENTAL[6]

PLANT EXTRACTION.—The bark of *Canella winterana* was purchased from Meer Corporation, lot ≠7-9242-0, and was obtained in January, 1978. The plant material (750 g) was ground in a blender then extracted by cold percolation with 95% ethanol. The alcoholic extract was evaporated *in vacuo* at 40° to leave 193 g of dark brown syrupy residue that deposited numerous crystals of mannitol. This residue was dissolved in 500 ml of chloroform, and the chloroform layer was washed with four-125 ml portions of water. The combined water phases were back-washed with 25 ml of chloroform, and the combined chloroformic phase and washing was dried over anhydrous sodium sulfate then evaporated to leave 156 g of an oily residue. For further partitioning the residue was dissolved in 600 ml 90% methanol then washed with three-200 ml portions of *n*-hexane. Evaporation of the methanolic phase left 87 g of residue.

ISOLATION OF 3-METHOXY-4,5-METHYLENEDIOXYCINNAMALDEHYDE (**1**) AND CANELLAL (**2**).— The 90% methanol solubles obtained above (10 g) were chromatographed on a column 48 x 4.5 cm, of silica gel (400 g) packed in chloroform. Seventy-five ml fractions were collected and each fraction was evaporated and the residue weighed. Fractions 25–29 yielded 0.151 g of a yellow crystalline residue that was recrystallized from ether-hexane to give yellow needles of **1**, mp 136–137°; optically inactive; ir νmax (CHCl₃) 1675, 1630, 1600 and 1124 cm⁻¹; uv λmax (MeOH) 337 nm (ε=11,000) and 243 nm (ε=10,800); pmr δ(CDCl₃) 9.66 (d, 1H, J=7.8 Hz), 7.31 (d, 1H, J=16.2 Hz), 6.64 and 6.37 (2d, 1H, J=7.8 and 16.2 Hz), 6.73 (s, 2H), 6.02 (s, 2H), and 3.93 (s, 3H); ¹³C nmr δ(CDCl₃) 193.0 (1d), 152.2 (d), 149.8 (s), 144.0 (s), 138.5 (s), 129.1 (s), 127.5 (d), 110.3 (d), 102.2 (t), 101.9 (d) and 56.9 (q); ms M+ at m/e 206 (42%) with the base peak at m/e 133.

Calculated for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.10; H, 4.99.

Fraction 31 yielded, upon evaporation, 7 mg of canellal **2** identical with the material previously reported (2). This is, however, an abnormally low yield for this collection of plant material; approximately 300 mg or more should have been obtained.

BOROHYDRIDE REDUCTION OF **1** TO **3**.—In 10 ml of absolute ethanol, 100 mg of **1** and 1.0 g of polymer-supported borohydride were stirred for 2 hours. The progress of reaction was monitored by thin layer chromatographic analysis on silica gel G plates with chloroform as solvent. The starting material gave a spot R_f 0.70 while the product **3** gave a spot, R_f 0.30. The reaction mixture was filtered and the resin beads were washed with about 50 ml of absolute alcohol. Evaporation of the solvent left a crystalline residue (96 mg) that was recrystallized from an ethanol-ether mixture to give colorless needles of **3**, mp 83–84°; optically inactive, ir (CHCl₃) showed hydroxyl absorption bands at 3620 and 3460 cm⁻¹; pmr δ(CDCl₃) 6.03 (s, 2H), 4.33 (d, 2H), 3.95 (s, 3H), 2.28 (broad s, 1H, exchangeable) with the aromatic and vinylic protons overlapping between about 6.27–6.73; ¹³C nmr δ(CDCl₃) 149.4 (s), 143.8 (s), 135.3 (s), 132.0 (s), 131.0 (d), 127.7 (d), 107.5 (d), 101.6 (t), 100.3 (d), 63.6 (t) and 56.9 (q); ms M+ at m/e 208 (100%).

Calculated for $C_{11}H_{12}O_4$: C, 63.45; H, 5.82. Found: C, 63.46; H, 5.86.

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[5]This compound is commercially available from Tridom Chemical Inc.; however, the material actually used was synthesized by the procedure given in reference 8.

[6]All melting points were taken in capillaries on a Thomas Hoover Unimelt apparatus and are uncorrected. Uv spectra were taken on a Beckman model Acta III recording spectrophotometer; ir spectra were determined on either a Beckman IR-33 recording infrared spectrophotometer or a Perkin-Elmer 257 infrared spectrophotometer; optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter; ¹H nmr spectra were recorded on a JEOL model C-60 nuclear magnetic spectrometer at 60 MHz operating at room temperature with CDCl₃ as solvent and tetramethylsilane (TMS) as internal standard with chemical shifts reported as δ(ppm) values; the ¹³C nmr spectra were recorded on JNM-FX60 Fourier Transform nmr spectrometer at 15.06 MHz. Proton noise decoupled and/or off-resonance decoupled spectra were obtained with CDCl₃ as solvent and TMS as internal standards. High and low resolution mass spectra were taken on an E. I. Dupont de Nemours model 21-492 mass spectrometer. Elemental analyses were done by Scandinavian Microanalytical Laboratory in Herlev, Denmark. Spot detection on tlc plates was achieved by spraying with 0.5% aqueous KMnO₄ or by viewing under ultraviolet light.

CATALYTIC HYDROGENATION OF **3** TO **4**.—Compound **3** (150 mg) was dissolved in 2 ml of absolute ethanol, and the solution was added to a suspension of 50 mg 5% palladium on charcoal presaturated with hydrogen. The mixture was stirred under a hydrogen atmosphere until the hydrogen uptake ceased (45 minutes). Filtration of the mixture and evaporation of the filtrate left 152 mg of a colorless oily residue that was homogeneous on thin layer chromatographic analysis on silica gel G plates with chloroform being used as solvent. The tlc gave a spot R_f 0.28. The ir (CHCl$_3$) spectrum showed hydroxyl absorption bands at νmax 3620 and 3470 cm^{-1}; pmr δ(CDCl$_3$) 6.38 (s, 2H), 5.92 (s, 2H), 39 (s, 3H), 3.67 (t, 3H) and the 6 protons of the side chain absorbed between 1.7–2.76; ^{13}C nmr δ(CDCl$_3$) 149.1 (s), 143.6 (s), 136.6 (s), 135.5 (s), 108.2 (d), 102.6 (d), 101.2 (t), 62.0 (t), 56.8 (q), 34.4 (t) and 32.2 (t); ms M+ at m/e 210 (46%) with the base peak at m/e 165.

METHYLENATION OF 5-HYDROXYVANILLIN.—The starting material for this reaction, 5-hydroxyvanillin, was either obtained from Tridom Chemical Inc. or synthesized from 5-iodo-vanillin (obtained from Aldrich Chemical Co.) by the previously reported procedure (6). Therefore, 5-hydroxyvanillin (1.0 g) was dissolved in a solution of sodium hydroxide (0.8 g) in 3 ml of water. The solution was added over a two-hour period to a mixture of 2 ml of methylene bromide, 2 ml of water and two drops of Adogen 464 while being refluxed under a nitrogen atmosphere. After complete addition of the phenol solution, the mixture was re-fluxed for one more hour then cooled and extracted with three 150 ml portions of benzene. Evaporation of the combined benzene extracts left a brown residue which was dissolved in chloroform and passed through a column of 50 g silica gel. Most of the brown material stayed on the column; the eluate, however, retained a yellow color and, upon evaporation, left a yellow crystalline residue (0.96 g) which was essentially one spot, R_f 0.25, on thin layer chromatographic analysis on silica gel G plates using chloroform as solvent. Further purification of this material was achieved by either chromatography on a silica gel G column with chloroform as solvent or by crystallization from benzene-isopropyl ether mixture to give colorless needles of myristicin aldehyde (**6**) mp 131–132° [literature (7) mp 131–132°]. Its spectral properties were in agreement with the expected structure.

CONVERSION OF **5** to **1**.—Compound **5** obtained from myristicin aldehyde by the already reported procedure (4) was first converted to the acid chloride by refluxing 250 mg in a solution of 3 ml of thionyl chloride in 3 ml of benzene containing one drop of dimethylformamide (there was NO reaction without it). After ninety minutes, the mixture was evaporated; the residue was dissolved in benzene and evaporated again. This procedure was repeated for four times, then the residue was finally dissolved in 5 ml of acetone. The solution was stirred for eighty minutes with 785 mg of bis(triphenylphosphine)-tetrahydroborate copper I (8). Evaporation of the acetone left 327 mg of a crude mixture which was purified by chromatography on a column, 45 x 2.7 cm of silica gel G (80 g) with hexane-chloroform (1:4) as the solvent system. The product was obtained as yellow needles (205 mg) indistinguishable from the natural product (undepressed mixed melting point and superimposable ir and pmr spectra).

ACKNOWLEDGMENT

LITERATURE CITED

1. M. Windholz (editor), "The Merck Index," Nineth Edition, Merck and Co., Inc., Rahway, N.J., 1976, p. 221.
2. F. S. El-Feraly, A. T. McPhail and K. D. Onan, *J. Chem. Soc. Chem. Comm.*, 75 (1978).
3. F. L. Johnson and W. C. Jankowski, "Carbon-β NMR Spectra, a Collection of Assigned, Coded and Indexed Spectra," published by Wiley Interscience, New York, N.Y., Spectrum number 336.
4. R. A. Surry, *J. Amer. Chem. Soc.*, **70**, 2887 (1948), and references therein.
5. R. Olstein and E. F. M. Stephenson, *Aust. J. Chem.*, **32**, 681 (1979).
6. S. K. Baneyee, M. Manolopoulo and J. M. Pepper, *Canad. J. Chem.*, **40**, 2175 (1962).
7. K. N. Campbell, P. F. Hopper and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).
8. T. N. Sorrell and R. J. Spillane, *Tetrahedron Lett.*, 2473 (1978).