[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# REACTIONS OF VANILLIN AND ITS DERIVED COMPOUNDS. XI.[1] CINNAMIC ACIDS DERIVED FROM VANILLIN AND ITS RELATED COMPOUNDS[2, 3]

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In continuing our studies on the toxicities and ultraviolet absorption characteristics of esters of vanillic and related acids, it was desired to investigate the substituted cinnamic acids related to vanillin. These cinnamic acids are easily prepared by condensation of the desired aldehyde with malonic acid in the presence of a trace of piperidine with pyridine as a solvent, in accordance with the Doebner modification of the Perkin reaction. The actual procedure employed in this study is an adaptation of the above reaction made by Vorsatz (1) for the preparation of cinnamic acids having a free phenolic group, and is recommended by Johnson (2) for the preparation of ferulic acid. The Vorsatz adaptation employs long standing at room temperature instead of the short boiling originally used by Doebner (3). We have found this modification to be equally satisfactory for the preparation of nonphenolic cinnamic acids. In this study cinnamic acids were prepared from the following aldehydes: vanillin, veratraldehyde, 5-nitrovanillin, 5-chlorovanillin, *o*-benzylvanillin, piperonal, and orthovanillin. Only in the case of the 5-nitrovanillin was heating necessary to obtain reaction. The reaction of orthovanillin with malonic acid in the Vorsatz procedure yielded a crystalline compound melting at 119–120°, the structure of which was not ascertained, but which yielded orthoferulic acid when boiled with alkali or when allowed to stand for an extended period. No trace of a coumarin or coumarincarboxylic acid was obtained.

These acids were esterified with anhydrous ethanol in the presence of sulfuric acid to give good yields of the ethyl esters. Data for the acid and the ester preparations are found in Table I (references to earlier preparations are included). The inhibiting concentrations of the esters were determined for the four representative aerobic microörganisms—namely, non-sporeforming- (*Aerobacter aerogenes*) and sporeforming- (*Bacillus mycoides*) bacteria and molds (*Aspergillus niger* and *Penicillium glaucum*). The results are also given in Table I.

The toxicities of the ethyl esters of these substituted cinnamic acids toward the above noted representative microörganisms were universally poor and much lower than those of the corresponding benzoic acid esters. Only the benzyl ether of ethyl ferulate was toxic to *Aerobacter aerogenes* at a concentration as high as

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0.21%. None of the esters was toxic to the two molds at this concentration. All the ethers of ethyl 3,4-dihydroxycinnamate were toxic toward *Bacillus mycoides* at a concentration of 0.21% and ethyl 3,4-dimethoxycinnamate was toxic at a concentration as low as 0.09%.

TABLE I

SUBSTITUTED CINNAMIC ACIDS AND THEIR ETHYL ESTERS

| SUBSTITUENTS | ACIDS |  | ETHYL ESTERS |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | Yield, % | M.P., °C. | Yield, % | M.P., °C. | Formula | Analyses, C |  | H |  | Inhibiting concn.,[a] % |  |
|  |  |  |  |  |  | Calc'd | Found | Calc'd | Found | *Aero. aero.* | *Bac. myc.* |
| 4-Hydroxy-3-methoxy (1) | 85 | 174[b] | 77[c] | 38[d,e] | $C_{12}H_{14}O_4$ | 64.85 | 64.80 | 6.35 | 6.45 | 0.21 | 0.21 |
| 3,4-Dimethoxy(8) | 94 | 186[f] | 63 | 52[d] |  |  |  |  |  | .21 | .09 |
| 3,4-Methylenedioxy (1, 9) | 97[g] | 247[f] | 78 | 67[d] |  |  |  |  |  | .21 | .21 |
| 4-Benzyloxy-3-methoxy (10) | 93[h] | 191[f] | 80 | 64[i] | $C_{19}H_{20}O_4$ | 73.05 | 73.00 | 6.46 | 6.47 | .21 | .21 |
| 4-Hydroxy-3-methoxy-5-chloro | 98[j] | 251[k] | 97 | 106[i] | $C_{12}H_{13}ClO_4$ | 56.15 | 56.01 | 5.10 | 5.16 | .21 | .21 |
| 4-Hydroxy-3-methoxy-5-nitro | 90[l] | 249[m] | 75 | 141[f] | $C_{12}H_{13}NO_6$ | 54.11 | 54.15 | 4.95 | 4.98 | .21 | .21 |

[a] Inhibiting concentrations were determined in accordance with the method described earlier [Pearl and McCoy, *J. Am. Chem. Soc.*, **69**, 3071 (1947)]. Abbreviations used: *Aero. aero.* = *Aerobacter aerogenes*; *Bac. myc.* = *Bacillus mycoides*. The inhibiting concentration against *Aspergillus niger* and *Penicillium glaucum* was greater than 0.21% in all cases. [b] From dilute ethanol. [c] The product was obtained as a colorless oil boiling at 185°/3.5 mm., $n_D^{30}$ 1.5911. On standing, the oil crystallized. [d] From petroleum ether (b.p. 65–110°). [e] Tanaka [*Science Repts. Tôhoku Imp. Univ., First Ser.*, **18**, 619 (1929)] reported a melting point of 75.5–76.5° for ethyl ferulate containing one molecule of water. [f] From ethanol. [g] Short refluxing (1.5 hours) was necessary for complete reaction. [h] The reaction mixture was refluxed for 2.5 hours and allowed to stand 16 hours. [i] From dilute methanol. [j] The reaction mixture was allowed to stand for 19 days. [k] *Anal.* Calc'd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.96. Found: C, 52.63; H, 4.00. Raiford and Lichty [*J. Am. Chem. Soc.*, **52**, 4576 (1930)] reported 235–236° for the melting point of the product obtained by the Perkin reaction of 5-chlorovanillin. [l] The reaction mixture was heated on the steam-bath under reflux for 2 hours after standing 6 days at room temperature. [m] *Anal.* Calc'd for $C_{10}H_9NO_6$: N, 5.85. Found: N, 5.80. Kürschner and Peikert [*Zellstoff-Faser*, **32**, no. 2, 19 (1935)] treated 5-nitrovanillin with acetic anhydride and sodium acetate and obtained a product melting at 175°, which they also reported as 4-hydroxy-3-methoxy-5-nitrocinnamic acid. Obviously it was different from the present product.

The ultraviolet absorption spectra of these compounds were determined in 95% ethanol with a Beckman spectrophotometer at minimum slit width. The spectra of the acids of Table I are reproduced in Figures 1 and 2. It is obvious from Figure 1 that the various ethers of 3,4-dihydroxycinnamic acid have essentially the same basic ultraviolet absorption spectra with principal maxima at approximately 2200 and 3200 Å and a principal minimum at approximately 2600 Å. The effect of a change in the ether groups upon the secondary maxima on both principal bands is clearly evident. In Figure 2 the spectra of 5-chloro- and 5-nitro-ferulic acids and orthoferulic acid are reproduced. Substitution of the 5-hydrogen by chlorine does not produce much change in the basic spectrum of ferulic acid, but substitution by the nitro group results in a hypsochromic shift of the entire spectrum. The curve for orthoferulic acid is reminiscent of the parent curve for orthovanillin (4). In fact, all the spectra pictured in Figures 1 and 2 have striking resemblance to those of the parent benzaldehydes (4) and not to those of the corresponding benzoic acids.

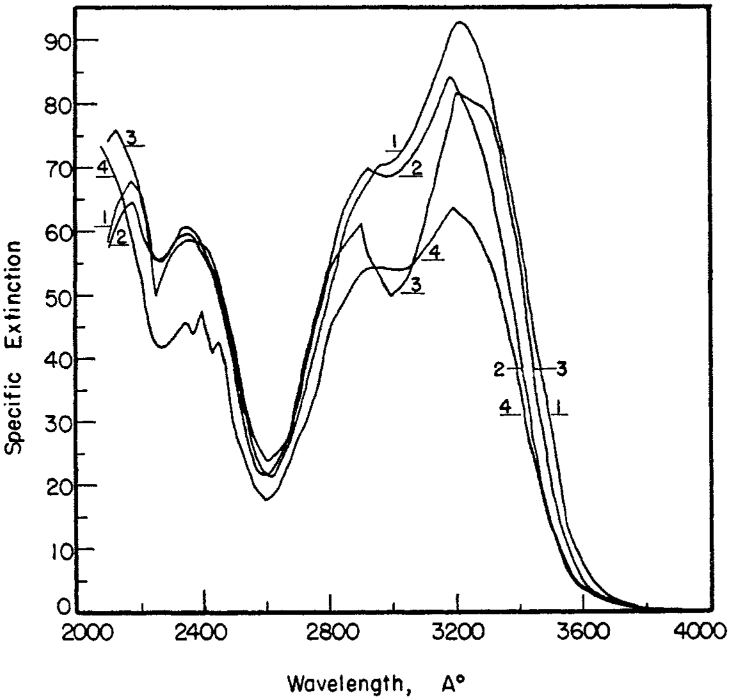

Fig. 1. Ultraviolet Absorption Curves for Substituted Cinnamic Acids. 1. 4-Hydroxy-3-methoxycinnamic acid; 2. 3,4-Dimethoxycinnamic acid; 3. 3,4-Methylenedioxycinnamic acid; 4. 4-Benzyloxy-3-methoxycinnamic acid.

The spectra for the ethyl esters of the acids given in Figure 1 and 2 are identical with those of the parent acids except for actual extinction values.

## EXPERIMENTAL

All melting points given are uncorrected.

*Starting materials.* Vanillin and piperonal were purified commercial products. Orthovanillin was the technical product of the Monsanto Chemical Company but was recrystallized before use. Veratraldehyde was prepared in 90% yield according to the method of Barger and Silberschmidt (5); it melted at 43-44°. *o*-Benzylvanillin was obtained in 95% yield by a modification of the process reported by Späth, Orekhov, and Kuffner (6) for the preparation of *o*-benzylisovanillin. 5-Chlorovanillin was obtained by the methods of Menke and Bentley (7).

*5-Nitrovanillin.* This compound was prepared in the following manner. In a 2-liter, 3-necked-flask equipped with a thermometer, dropping-funnel, and stirrer, was placed a solution of 100 g. of vanillin in 500 cc. of glacial acetic acid. The flask was placed in an ice-salt bath. When the temperature of the solution reached 11°, 40 cc. of fuming nitric acid (*sp. gr.* 1.5) was added dropwise over a period of 35 minutes. The temperature was maintained below 16° during the entire addition. After all the nitric acid was added, the mixture was filtered, and the yellow precipitate was washed with cold methanol and allowed to air-dry. A yield of 107 g. (83%) of 5-nitrovanillin melting at 175–176° was obtained.

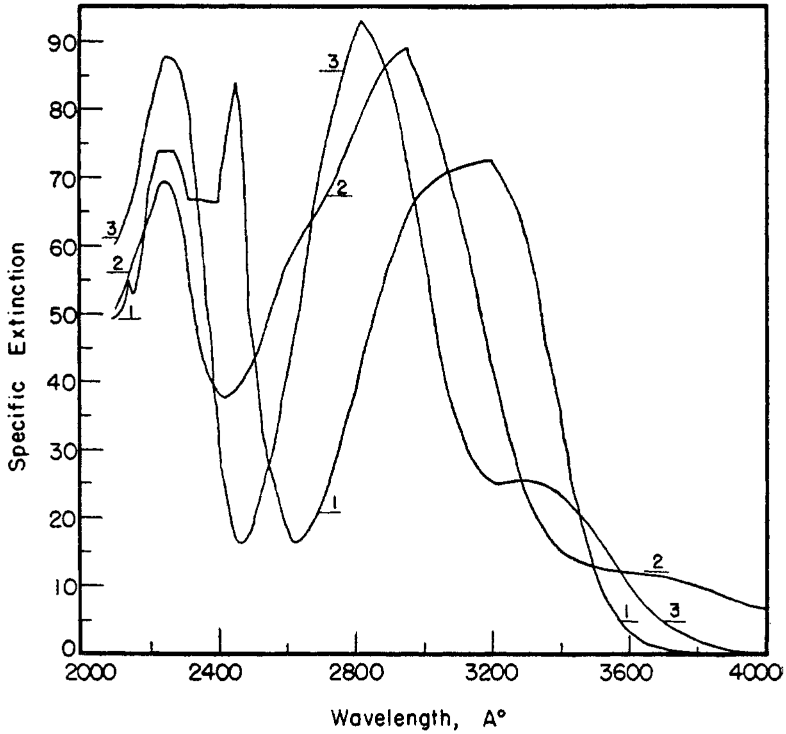

FIG. 2. ULTRAVIOLET ABSORPTION CURVES FOR SUBSTITUTED CINNAMIC ACIDS. 1. 5-Chloro-4-hydroxy-3-methoxycinnamic acid; 2. 5-Nitro-4-hydroxy-3-methoxycinnamic acid; 3. 2-Hydroxy-3-methoxycinnamic acid.

*Preparation of substituted cinnamic acids.* A solution of 304 g. (20 moles) of vanillin, 460 g. (4.4 moles) of malonic acid, 20 g. of piperidine (0.24 mole), and 1000 cc. of dry pyridine was allowed to stand in the dark at room temperature, protected with a soda-lime tube. After three weeks, the mixture was stirred into a solution of 1200 cc. of concentrated hydrochloric acid and 2000 g. of chopped ice. The heavy precipitate was filtered, washed with 5% hydrochloric acid and with water, and air-dried. The yield of ferulic acid (3-methoxy-4-hydroxycinnamic acid) melting at 174° was 304 g. or 85%. The compounds listed in Table 1 were prepared by essentially the same reaction. Major variations are noted.

*Reaction of orthovanillin with malonic acid.* A reaction mixture identical with the above, but employing orthovanillin (2-hydroxy-3-methoxybenzaldehyde) in place of vanillin, was allowed to stand for 3 weeks and then stirred into the hydrochloric acid-ice mixture. The clear solution which resulted was extracted with ether, and the ether was dried and distilled under reduced pressure. The residual viscous yellow oil solidified upon standing. Recrystallization from benzene yielded 108 g. of crystals melting at 119–120° which were not identified.

*Anal.* Found: C, 58.2; H, 5.67; $CH_3O$, 11.1.

Upon standing for an extended period or upon boiling with dilute sodium hydroxide, acidifying, and recrystallizing the precipitate from very dilute ethanol, orthoferulic acid is obtained as colorless crystals melting sharply at 186–187°.

*Anal.* Calc'd for $C_{10}H_{10}O_4$: $CH_3O$, 16.0. Found: $CH_3O$, 16.0.

*Preparation of substituted cinnamic acid esters.* A mixture of 50 g. of 3,4-methylenedioxycinnamic acid, 500 cc. of absolute ethanol, and 10 cc. of concentrated sulfuric acid was refluxed for 6 hours. Approximately 300 cc. of excess solvent was removed and the residue was poured into 3 liters of cold water and neutralized with a slurry of sodium bicarbonate. The precipitate was filtered, washed, and dried to give 45 g. (78%) of ethyl 3,4-methylenedioxycinnamate melting at 62°. Recrystallization from petroleum ether (b.p. 65–110°) yielded colorless crystals melting at 67°. The ethyl esters listed in Table I were prepared by the same procedure.

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## SUMMARY

A number of old and new substituted cinnamic acids have been prepared from vanillin and some of its related compounds by the Vorsatz modification of the Doebner reaction. The ethyl esters of these substituted cinnamic acids were prepared and their inhibiting concentrations were determined for the representative microörganisms *Aerobacter aerogenes*, *Bacillus mycoides*, *Aspergillus niger*, and *Penicillium glaucum*. The ultraviolet absorption spectra of these compounds have been determined.

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