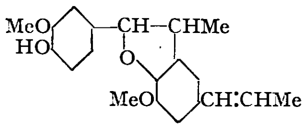
# 147. *The Constituents of Natural Phenolic Resins. Part XIX. The Oxidation of Ferulic Acid.*

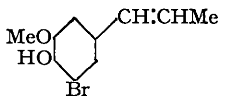
By Neville J. Cartwright and Robert D. Haworth.

It has previously been suggested that the lignans are derived by oxidative coupling of *n*-propenylphenol derivatives at the *β*-carbon atom of the side chain. This type of oxidative coupling has now been experimentally realised by the conversion of ferulic acid into " dehydrodiferulic acid " (20% yields) by the action of either ferric chloride or ammonium persulphate. Constitution (III; R = H) assigned to the oxidation product has been established by hydrolysis of the dimethyl ether to veratraldehyde and veratrylidenesuccinic acid, and also by cyclisation and dehydrogenation to the anhydride of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)-naphthalene-2 : 3-dicarboxylic acid.

The oxidation of phenols to peroxides (Pummerer, *Ber.*, 1914, **47**, 1472; Goldschmidt and Schmidt, *ibid.*, 1922, **55**, 3197), diphenyl ethers (Pummerer, *ibid.*, 1925, **58**, 1808; Erdtman, *Svensk. Kem. Tids.*, 1934, **46**, 226), 2 : 2′- or 4 : 4′-dihydroxydiphenyls (Dianin, *Ber.*, 1873, **6**, 1252; Tiemann, *ibid.*, 1885, **18**, 3493; Cousin and Heressey, *Bull. Soc. chim.*, 1908, **3**, 1066, 1070) involves coupling at the anionoid centres of the molecules. The β-carbon atom of the side chain of a *p*-hydroxypropenylbenzene may acquire this character in virtue of the extended conjugation and analogous coupling may be expected. The oxidation of *iso*eugenol to dehydro*iso*eugenol (I) (Erdtman, *Annalen*, 1933, **503**, 283) involves a union between the anionoid centre of the side chain and the *o*-position with respect to the phenolic group in a second molecule. The suggestion (J., 1942, 455) that natural lignans are derived from two *p*-hydroxypropenylbenzene molecules by oxidation at the β-carbon atom in the side chain arose from a further application of these views, but no examples of such coupling have been reported previously.

(I.)

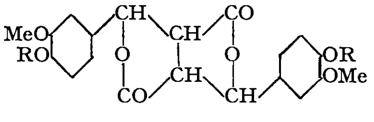


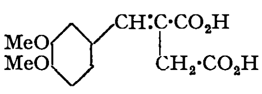


(II.)

5-Bromo*iso*eugenol (II), in which the reactive nuclear positions were not available, appeared to be a favourable case for the realisation of side-chain union. 5-Bromovanillin (Tiemann and Haarmann, *Ber.*, 1874, **7**, 615) was converted by treatment with ethylmagnesium iodide into *α-(5-bromo-4-hydroxy-3-methoxyphenyl)-propyl alcohol*, but dehydration of this to 5-bromo*iso*eugenol (II) presented difficulties. In a few experiments the dehydration was successfully accomplished by the action of excess of ethylmagnesium iodide, but the yields were very variable, and excessive polymerisation occurred when alternative dehydrating agents were selected. It was then discovered that ferulic acid (4-hydroxy-3-methoxycinnamic acid) was oxidised by ferric chloride in aqueous-alcoholic solution. A brown ferric salt gradually separated, which was decomposed by acids to a crystalline substance, $C_{20}H_{18}O_8$, m. p. 211° (decomp.). After the completion of our experiments it was found that Erdtman (*Svensk. Kem. Tids.*, 1935, **47**, 223) had previously obtained 9% yields of the same compound, " dehydrodiferulic acid," by a similar method, but apart from suggesting that the compound was an alkali-unstable phenolic lactone of the above composition, he was unable to elucidate the structure with the material at his disposal. We have shown that this compound may be obtained in 20% yield by oxidising ferulic acid with ammonium persulphate, and also in 22% yield with ferric chloride in the presence of an air stream. " Dehydrodiferulic acid " has consequently been made readily available, and a detailed examination has proved it to be the *dilactone* (III; R = H) of 1 : 4-*dihydroxy*-1 : 4-*di*-(4′-*hydroxy*-3′-*methoxyphenyl*)*butane*-2 : 3-*dicarboxylic acid.* The analytical and molecular-weight values and the insolubility in sodium hydrogen carbonate solution are in agreement with this structure, and the phenolic nature is supported by the green ferric test, the formation of a *di*-p-*nitrobenzoyl* derivative, and the solubility in cold sodium hydroxide solution.

(III.)



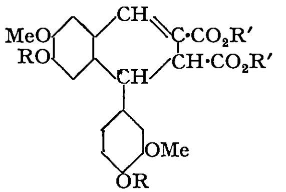


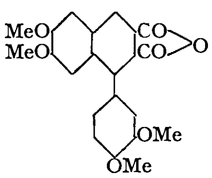
(IV.)

This reaction with sodium hydroxide, however, leads to considerable decomposition which was responsible for our failure to methylate the phenol with methyl sulphate in alkaline solution. The *dimethyl ether* (III; R = Me) was eventually prepared in high yield by the action of diazomethane on an acetone solution of the phenol (III; R = H). The ether gave no ferric test, and it was oxidised by alkaline potassium permanganate to veratric acid in 60% yield, thus establishing the presence of two veratryl groups in the lactone (III; R = Me). This dimethyl ether (III; R = Me) was insoluble in sodium hydrogen carbonate solution, but it dissolved with decomposition in boiling aqueous sodium hydroxide. When alcoholic sodium hydroxide was employed, the nature of the decomposition was easily traced to the production of a mixture of veratraldehyde (2 : 4-dinitrophenylhydrazone, m. p. 256°) and veratrylidenesuccinic acid (IV), m. p. 175°. The latter was identified by comparison with an authentic specimen (Stobbe, *Annalen*, 1911, **380**, 76), by conversion into the yellow anhydride (*idem, ibid.*), and by nitration to the *6-nitro-derivative*, m. p. 215°. The production of veratraldehyde and veratrylidenesuccinic acid from the ether (III; R = Me) represents the reversal of an aldol polymerisation reaction, and the degradation to veratrylidenesuccinic acid provides proof that the two ferulic units are linked at the β-carbon atoms of the side chain.

Further important evidence has been obtained from a study of the action of boiling methyl-alcoholic hydrogen chloride on the dimethyl ether (III; R = Me) and on " dehydrodiferulic acid " (III; R = H). In the former case cyclisation occurred with the production of *methyl* 6 : 7-*dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = R′ = Me). The same ester was also obtained by the action of diazomethane on *methyl* 7-*hydroxy*-6-*methoxy*-1-(4′-*hydroxy*-3′-*methoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V; R = H, R′ = Me), which was readily obtained by the action of methyl-alcoholic hydrogen chloride on " dehydrodiferulic acid." Alkaline hydrolysis of the methyl ester (V; R = R′ = Me) gave the

(V.)





(VI.)

corresponding dibasic *acid* (V; R = Me, R′ = H), which yielded a yellow *anhydride*, m. p. 234—235°, when treated with acetyl chloride. This anhydride was readily dehydrogenated to the anhydride (VI) of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid, m. p. 304°, by heating with palladium-black at 220°, and the identity of the product was established by comparison with a specimen of (VI) synthesised as described in Part II (J., 1935, 640).

In view of the above evidence, structure (III; R = H) is regarded as rigidly established, and the formation of " dehydrodiferulic acid " provides the first example of the oxidation of compounds of the *iso*eugenol type at the β-carbon atom of the side chain.

## EXPERIMENTAL.

α-(5-*Bromo*-4-*hydroxy*-3-*methoxyphenyl*)*propyl Alcohol*.—Ethylmagnesium iodide, prepared from magnesium (9·5 g.) and ethyl iodide (61 g.) in ethereal solution (150 c.c.), was gradually added to a solution of 5-bromovanillin (15 g.) in boiling benzene (200 c.c.). The mixture was refluxed for 1 hour, decomposed with dilute sulphuric acid, and the benzene layer was washed with sodium hydrogen sulphite solution, dried, and the solvent removed. The residual *carbinol*, m. p. 72—82°, crystallised from benzene or benzene–light petroleum (b. p. 60—80°) in clusters of needles, m. p. 88—89° (Found : C, 46·3; H, 5·2; Br, 30·5. $C_{10}H_{13}O_3Br$ requires C, 46·1; H, 5·0; Br, 30·6%), which gave a dark green ferric test.

5-*Bromo*-4-*acetoxy*-3-*methoxybenzaldehyde*, prepared by the action of acetic anhydride on 5-bromovanillin, crystallised from dilute acetic acid in colourless plates, m. p. 84° (Found : C, 44·0; H, 3·5. $C_{10}H_9O_4Br$ requires C, 43·9; H, 3·3%), and, on treatment with an ethereal solution of ethylmagnesium iodide (1·5 mols.), it was converted into an oil which yielded α-(5-bromo-4-hydroxy-3-methoxyphenyl)propyl alcohol on hydrolysis with alkali.

5-*Bromo*iso*eugenol* (II).—The above carbinol (4 g.) in ether (25 c.c.) was added to ethylmagnesium iodide prepared from magnesium (2·2 g.), ethyl iodide (14 g.), and ether (35 c.c.). The ether was removed, and the residue heated at 100° for 2 hours and decomposed with dilute sulphuric acid. The product, isolated with ether, was distilled at 0·6 mm.; the distillate (2·5 g.), b. p. 155—160/0·6 mm., solidified, and crystallised from light petroleum (b. p. 40—60°) in felted needles, m. p. 59—60° (Found : Br, 32·9. Calc. for $C_{10}H_{11}O_2Br$ : Br, 32·9%), which gave a green ferric test (Zincke and Hahn, *Annalen*, 1903, **329**, 15, describe 5-bromo*iso*eugenol as an amorphous powder which sinters and darkens on heating). The yields are very variable in the above dehydration reaction, but other dehydrating agents, including potassium hydrogen sulphate, acetic anhydride, phosphoric oxide, anhydrous oxalic acid, and magnesium methoxide, gave inferior results.

5-*Bromo*-4-*hydroxy*-3-*methoxycinnamic Acid* (5-*Bromoferulic Acid*).—5-Bromovanillin (25 g.), malonic acid (40 g.), piperidine (1 c.c.), and pyridine (50 c.c.) were heated for 1·5 hours on the steam-bath, cooled, and poured into a solution of concentrated sulphuric acid (25 c.c.) in water (150 c.c.). The precipitate (27 g.) was collected, and crystallised from glacial acetic acid or nitrobenzene in small needles, m. p. 246° (decomp.) (Found : C, 44·4; H, 3·6; Br, 29·5. $C_{10}H_9O_4Br$ requires C, 44·0; H, 3·3; Br, 29·3%), which gave a green colour with ferric chloride. The *ethyl* ester, prepared by treatment with alcohol (25 vols.) and concentrated sulphuric acid (4 parts), crystallised from alcohol in glistening needles, m. p. 129° (Found : C, 48·0; H, 4·3; Br, 27·2. $C_{12}H_{13}O_4Br$ requires C, 47·8; H 4·3; Br, 26·6%).

*Dilactone of* 1 : 4-*Dihydroxy*-1 : 4-*di*-(4′-*hydroxy*-3′-*methoxyphenyl*)*butane*-2 : 3-*dicarboxylic Acid* : " *Dehydrodiferulic Acid* " (III; R = H).—(*a*) A solution of 4-hydroxy-3-methoxycinnamic acid (40 g.) in methylated spirits (400 c.c.) was added during 15 minutes to a solution of crystalline ferric chloride (80 g.) in water (3,000 c.c.), stirred by a rapid stream of air. A chocolate-coloured precipitate gradually separated, and after 6 hours the air stream was stopped, and the reaction mixture set aside overnight. The ferric salt was collected as a paste, suspended in water (500 c.c.), heated to 70—80°, and decomposed by addition of concentrated hydrochloric acid (100 c.c.) with vigorous shaking. After cooling, the precipitate was collected, and coloured sticky material was removed by washing with ether. The residual white product, crystallised from acetone–methylated spirits, yielded plates (9 g.), m. p. 208—209° (decomp.).

(*b*) Ammonium persulphate (4·5 g.) was added to a solution of 4-hydroxy-3-methoxycinnamic acid (3·5 g.) in boiling water (200 c.c.) containing one drop of a saturated solution of ferrous sulphate. A pink colour developed, and the semi-solid product which separated on cooling crystallised from glacial acetic acid (charcoal) in plates (0·5 g.), m. p. 206—208°.

The *dilactone* (III; R = H), prepared by either method (*a*) or (*b*), separated from acetone–methylated spirits or glacial acetic acid in quadratic plates, m. p. 211° (decomp.) (Erdtman, *loc. cit.*, gives m. p. 202—205°, decomp.) [Found : C, 62·3; H, 4·6; *M* (Rast), 390. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%; *M*, 386]; it is almost insoluble in ether, sparingly soluble in alchol, but readily soluble in acetone or chloroform. It is readily soluble in cold sodium hydroxide, insoluble in sodium hydrogen carbonate solution, and gives a dark green ferric test. The *dinitrobenzoate* was prepared by refluxing for ½ hour a solution of the dilactone (III; R = H) (1 g.) and *p*-nitrobenzoyl chloride (1·5 g.) in dry pyridine (15 c.c.); water was added, and the precipitate (1·5 g., m. p. 253—256°) was collected and crystallised from dioxan; small, pale yellow, irregular prisms, m. p. 257—258° (decomp.) (Found : N, 4·4. $C_{34}H_{24}O_{14}N_2$ requires N, 4·1%), were obtained.

*Dilactone of* 1 : 4-*Dihydroxy*-1 : 4-*di*-(3′ : 4′-*dimethoxyphenyl*)*butane*-2 : 3-*dicarboxylic Acid* (III ; R = Me).—An ethereal solution of diazomethane, prepared from *N*-nitrosomethylurethane (3·0 c.c.), was added to a solution of the phenolic dilactone (III ; R = H) (1 g.) in acetone (50 c.c.). After 24 hours, the excess of diazomethane was destroyed by addition of a few drops of concentrated hydrochloric acid. Most of the ether was removed, the residue was taken up in chloroform, washed with water and dilute sodium hydroxide solution, and recovered. The *dilactone* (III ; R = Me) crystallised from glacial acetic acid in colourless plates (0·9 g.), m. p. 207° [Found : C, 63·3 ; H, 5·3 ; *M* (Rast), 420 ; *M* (cryoscopically in nitrobenzene), 408. $C_{22}H_{22}O_8$ requires C, 63·7 ; H, 5·3% ; *M*, 414]. This ether (III ; R = Me), which gave a negative ferric test, could not be reduced with hydrogen in the presence of palladium–charcoal or platinic oxide. Veratric acid was obtained in 60% yield by oxidising (III ; R = Me) as follows : Methyl-alcoholic potassium hydroxide was gradually added to a suspension of the ether in boiling methyl alcohol (10 vols.) until a permanent alkaline reaction to phenolphthalein was obtained. Water was then added, and the alcohol was removed by distillation. Permanganate was then added in slight excess to the warm solution, and, after the excess had been destroyed with alcohol, the mixture was filtered, and the filtrate concentrated. Acidification yielded veratric acid, which was isolated with ether and crystallised from hot water. The 6 : 6′-*dinitro*-derivative of (III ; R = Me), obtained by addition of concentrated nitric acid (1·5 c.c.) in glacial acetic acid (1·5 c.c.) to a cold solution of (III ; R = Me) (0·5 g.) in glacial acetic acid (5 c.c.), was sparingly soluble in the usual organic solvents, but crystallised from anhydrous formic acid in pale yellow, felted needles, m. p. 265° (decomp.) (Found : C, 52·5 ; H, 4·0. $C_{22}H_{20}O_{12}N_2$ requires C, 52·4 ; H, 4·0%).

*Action of Potassium Hydroxide on the Ether* (III ; R = Me).—25% Methyl-alcoholic potassium hydroxide was added dropwise to a suspension of the methyl ether (1·5 g.) in boiling methyl alcohol (20 c.c.) until a permanent pink reaction was observed with phenolphthalein. 2N-Potassium hydroxide (20 c.c.) was then added, and after refluxing for 1 hour, the mixture was cooled, acidified, and extracted with chloroform. The extract was shaken with a saturated aqueous solution of sodium hydrogen carbonate and separated into an acid and a neutral fraction. Evaporation of the chloroform from the latter fraction gave an oil which was distilled at 12 mm. ; the distillate, which solidified on cooling, was identified as veratraldehyde by m. p., and by preparation of the 2 : 4-dinitrophenylhydrazone, which separated from ethyl acetate in orange-red prisms, m. p. 256°, undepressed by admixture with an authentic specimen (Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 760, gives m. p. 261—263°, corr.). The sodium hydrogen carbonate extract was acidified, and the acid product, isolated with chloroform, crystallised from benzene–methyl alcohol in small prisms (0·9 g.), m. p. 168—170°, raised to 175° by recrystallisation from hot water [Found : C, 58·8 ; H, 5·1 ; *M* (Rast), 270 ; equiv., 130. Calc. for $C_{13}H_{14}O_6$ : C, 58·6 ; H, 5·3% ; *M*, 266 ; equiv., 133]. The acid, identified as veratrylidenesuccinic acid (IV) by comparison with a specimen prepared by Stobbe's method (*loc. cit.*), was converted into the anhydride by refluxing with acetyl chloride; the anhydride separated from benzene either as orange prisms, m. p. 166°, containing benzene of crystallisation which was readily lost at 95°, or as unsolvated yellow prisms, m. p. 166° (Found on unsolvated material : C, 62·8 ; H, 4·8. Calc. for $C_{13}H_{12}O_5$ : C, 62·9 ; H, 4·9%). 6-*Nitroveratrylidenesuccinic acid*, prepared in quantitative yield by treating the acid (0·1 g.) in glacial acetic acid (2 c.c.) with concentrated nitric acid (1 c.c.), crystallised from dilute acetic acid in pale yellow, silky needles, m. p. 215° (decomp.) (Found : C, 50·0 ; H, 4·0 ; N, 4·5 ; equiv., 153. $C_{13}H_{13}O_8N$ requires C, 50·1 ; H, 4·2 ; N, 4·5% ; equiv., 155).

*Methyl* 7-*Hydroxy*-6-*methoxy*-1-(4′-*hydroxy*-3′-*methoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V ; R = H, R′ = Me).—The dilactone (III ; R = H) (1 g.) was refluxed for 2 hours with saturated methyl-alcoholic hydrogen chloride (25 c.c.). The mixture was diluted with water, and the *dimethyl* ester (V ; R = H, R′ = Me), isolated with chloroform, separated from glacial acetic acid in colourless prisms (1 g.), m. p. 203—205° (Found : C, 63·1 ; H, 5·0 ; OMe, 30·0. $C_{22}H_{22}O_8$ requires C, 63·7 ; H, 5·3 ; OMe, 29·9%), which gave a green ferric test, and a green fluorescence when a little water was added to its pyridine solution.

*Methyl* 6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate* (V ; R = R′ = Me).—(*a*) The methyl ether (III ; R = Me) (1 g.) was refluxed for 2 hours with methyl-alcoholic hydrogen chloride (25 c.c.). The mixture was diluted with water, and the *dimethyl* ester (V ; R = R′ = Me) (1 g.) was isolated with chloroform. (*b*) A solution of excess of diazomethane (1·2 g.) in ether (100 c.c.) was added to a solution of the ester (V ; R = H ; R′ = Me) (1 g.) in acetone (25 c.c.). After 3 days * a little concentrated hydrochloric acid was added, most of the ether was removed, and the product (1 g.) isolated with chloroform. The dimethyl ester (V ; R = R′ = Me) crystallised from methyl alcohol in hard prisms, m. p. 145° (Found : C, 64·7 ; H, 5·9 ; OMe, 43·0. $C_{24}H_{26}O_8$ requires C, 65·0 ; H, 5·9 ; OMe, 42·2%), which gave a negative ferric test.

6 : 7-*Dimethoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylic Acid* (V ; R = Me ; R′ = H).—The ester (V ; R = R′ = Me) was hydrolysed by refluxing for 2 hours with excess of 10% methyl-alcoholic potassium hydroxide ; water was added, and the methyl alcohol removed by distillation. After acidification, the *acid* (V ; R = Me ; R′ = H), isolated with chloroform in quantitative yield, crystallised from ethyl acetate in hard prisms, m. p. 134° (decomp.) (Found : C, 62·5 ; H, 5·5. $C_{22}H_{22}O_8,\frac{1}{2}CH_3{\cdot}CO_2Et$ requires C, 62·6 ; H, 5·7%), containing ethyl acetate which was eliminated on heating for 1 hour at 100° ; the residue had m. p. 154° (Found : C, 63·3 ; H, 5·3 ; equiv., 208. $C_{22}H_{22}O_8$ requires C, 63·7 ; H, 5·3% ; equiv., 207). The acid (V ; R = Me, R′ = H) was converted into the ester (V ; R = R′ = Me), m. p. 145°, by heating with methyl-alcoholic hydrogen chloride. The *anhydride* of the acid (V ; R = Me ; R′ = H), prepared by the action of acetyl chloride, crystallised from glacial acetic acid in glistening yellow leaflets, m. p. 234—235° (Found : C, 66·0 ; H, 5·2. $C_{22}H_{20}O_7$ requires C, 66·5 ; H, 5·1%). The acid (V ; R = Me ; R′ = H) or the anhydride, m. p. 235° (0·1 g.), was heated with palladium-black (0·02 g.) at 220° for 1 hour ; sublimation for 2 hours at 250—270°/0·4 mm. yielded the anhydride (VI) of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboxylic acid, which crystallised from nitrobenzene in pale yellow plates, m. p. 304°, undepressed on admixture with an authentic specimen (J., 1935, 640). The anhydride (VI) dissolved slowly in hot dilute sodium hydroxide solution ; careful acidification yielded the corresponding dibasic acid, which separated from methyl alcohol in small colourless needles, m. p. 232—234° (decomp.), unchanged on admixture with an authentic specimen of 6 : 7-dimethoxy-1-(3′ : 4′-dimethoxyphenyl)naphthalene-2 : 3-dicarboyxlic acid.

Our thanks are due to the West Riding Education Committee for a scholarship, and to Imperial Chemical Industries Limited (Dyestuffs Division) for assistance.

THE UNIVERSITY, SHEFFIELD 10. [*Received, April 3rd,* 1944.]

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* In some experiments using less diazomethane and a shorter reaction time a product, probably *methyl* 7-*hydroxy*-6-*methoxy*-1-(3′ : 4′-*dimethoxyphenyl*)-1 : 2-*dihydronaphthalene*-2 : 3-*dicarboxylate*, crystallising from methyl alcohol in colourless prisms, m. p. 179—180° (Found : C, 64·0 ; H, 5·6 ; OMe, 37·0. $C_{23}H_{24}O_8$ requires C, 64·3 ; H, 5·6 ; OMe, 36·2%), was obtained. This alkali-insoluble compound gave a negative ferric test and on methylation with excess diazomethane in ether–acetone solution was converted into the dimethyl ester (V ; R = R′ = Me), m. p. 145°.