cupric acetate monohydrate and 500 cc. of dry pyridine was carried out at 55° as described above, except that the heating time was only 1.5 hr. The mixture was cooled, filtered, and the solid was extracted in a Soxhlet apparatus with boiling benzene until no further material was extracted (this procedure was found necessary to obtain a good recovery of organic product). Isolation was then carried out as previously. The resulting total product (5.25 g.) was dissolved in 30 cc. of benzene and chromatographed on 1 kg. of alumina. The column was washed first with petroleum ether, then with various mixtures of petroleum ether–benzene and finally with benzene, 40-cc. fractions being collected.

Fractions 127–140, eluted with petroleum ether–benzene (2:3), consisted of the cyclic trimer cycloheneicosa-1,3,8,-10,15,17-hexayne (Vc) (0.145 g., 3.0%), m.p. 170–175°. Crystallization from ether yielded a pure sample with m.p. 174–175°; λ_{max} 228, 242 and 256 mμ (ε, 1120, 1160 and 840, respectively).

Anal. Calcd. for $C_{21}H_{18}$: C, 93.29; H, 6.71. Found: C, 92.88; H, 6.91.

Full hydrogenation of Vc and crystallization of the product from methanol–ethyl acetate yielded the new cycloheneicosane (VIc) with m.p. 63–64°.

Anal. Calcd. for $C_{21}H_{42}$: C, 85.63; H, 14.37; mol. wt., 295. Found: C, 85.66; H, 14.30; mol. wt., 289.

Fractions 144–152, also eluted with petroleum ether–benzene (2:3), consisted of the cyclic tetramer cycloöctacosa-1,3,8,10,15,17,22,24-octayne (VIIc) (0.185 g., 3.8%), m.p. 206–212°. Crystallization from ether gave the analytical sample with m.p. 213–214°; λ_{max} 226, 241 and 255 μ.

Anal. Calcd. for $C_{28}H_{24}$: C, 93.29; H, 6.71. Found: C, 92.98; H, 6.90.

Full hydrogenation of VIIc followed by crystallization of the product from methanol–ethyl acetate gave cycloöctacosane (VIIIc) with m.p. 47–48°, reported[7,9] m.p. 47–48°.

Anal. Calcd. for $C_{28}H_{56}$: mol. wt., 393. Found: mol. wt., 389.

Fractions 160–240, eluted with petroleum ether–benzene (2:3 to 1:3), consisted of an oil (0.51 g.) which crystallized in part. Fractions 246–265, eluted with benzene, on crystallization from ether yielded 0.055 g. of a substance with m.p. 97–98°, which rapidly became blue in light. The infrared spectra of both these materials (bands at 4.46 and 4.64 μ, no bands at 3.03 or 4.75 μ) showed them to be cyclic, but they have not been investigated further.

Oxidative Coupling of Deca-1,9-diyne (IId).—The coupling of 5 g. of deca-1,9-diyne (IId)[13c] with 75 g. of neutral cupric acetate monohydrate and 500 cc. of dry pyridine was performed as described above for octa-1,7-diyne (IIa). The total product (5.2 g.) showed only a weak band at 3.02 μ (terminal acetylene) in the infrared. It was dissolved in 30 cc. of benzene and chromatographed on 1 kg. of alumina. The column was washed successively with petroleum ether, various mixtures of petroleum ether–ether and finally with pure ether, 100-cc. fractions being collected.

Fractions 44–57, eluted with petroleum ether–ether (92.5:-7.5), consisted of the cyclic dimer cycloeicosa-1,3,11,13-tetrayne (IIId) (0.142 g., 2.9%), m.p. 78–80°. Crystallization from petroleum ether yielded the analytical sample as needles with m.p. 81–82°; λ_{max} 226, 240 and 254 mμ (ε, 870, 850 and 520, respectively).

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 90.57; H, 8.82.

Full hydrogenation of IIId and subsequent crystallization from methanol–ethyl acetate yielded the new cycloeicosane (IVd) with m.p. 61–62°.

Anal. Calcd. for $C_{20}H_{40}$: C, 85.63; H, 14.37; mol. wt., 281. Found: C, 85.73; H, 14.05; mol. wt., 270.

Fractions 81–99, eluted with petroleum ether–ether (85:15), contained a linear compound (strong band at 3.03 μ in the infrared) and were not investigated further.

Fractions 119–139, eluted with petroleum ether–ether (80:20), consisted of the cyclic trimer cyclotriaconta-1,3,-11,13,21,23-hexayne (Vd) (0.166 g., 3.4%), m.p. 128–134°. Crystallization from petroleum ether gave a pure sample as needles with m.p. 135–136°; λ_{max} 226, 240 and 254 mμ (ε 1030, 1030 and 620, respectively).

Anal. Calcd. for $C_{30}H_{36}$: C, 90.85; H, 9.15. Found: C, 90.50; H, 9.37.

Full hydrogenation of Vd and crystallization from methanol–ethyl acetate furnished cyclotriacontane (VId) with m.p. 57–58°, strongly depressed on admixture with the above-described cycloeicosane (IVd); reported[9] m.p. 57–58°.

Anal. Calcd. for $C_{30}H_{60}$: mol. wt., 421. Found: mol. wt., 416.

Fractions 166–186, eluted with petroleum ether–ether (70:30), consisted of the cyclic tetramer cyclotetraconta-1,3,11,13,21,23,31,33-octayne (VIId) (0.110 g., 2.2%), m.p. 146–150°. Crystallization from benzene–petroleum ether gave the analytical sample as plates with m.p. 152–154°; λ_{max} 226, 239 and 254 mμ. The m.p. was depressed on admixture with the cyclic trimer Vd.

Anal. Calcd. for $C_{40}H_{48}$: C, 90.85; H, 9.15. Found: C, 90.19; H, 8.93.

Full hydrogenation of VIId and crystallization from methanol–ethyl acetate yielded cyclotetracontane (VIIId) with m.p. 76.5–77°, undepressed on admixture with the sample obtained by the full hydrogenation of the cyclic pentamer IXa of octa-1,7-diyne (see above).

The last chromatographic fractions again contained crystalline higher cyclic polyacetylenes (no band at 3.03 μ in the infrared) which have not yet been investigated further.

Full Hydrogenations.—All full hydrogenations were carried out by shaking the cyclic polyacetylene (*ca.* 25 mg.), dissolved in 10 cc. of dioxane, in hydrogen over *ca.* 50 mg. of a prereduced platinum catalyst at room temperature and atmospheric pressure. When no more gas was absorbed, the catalyst was removed by filtration, washed well with hot dioxane, and the solvent was evaporated. The crystalline residue was dissolved in a little pentane (or benzene for the higher molecular weight hydrocarbons) and filtered through *ca.* 1 g. of alumina. The solvent was again evaporated and the residue crystallized from the specified solvent.

REHOVOTH, ISRAEL

[CONTRIBUTION FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, A LABORATORY OF THE WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Plant Polyphenols. VI. Experiments on the Synthesis of 3,3′- and 4,4′-Di-O-Methylellagic Acid[1]

BY LEONARD JURD

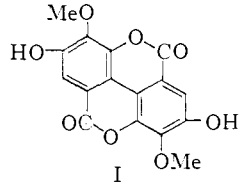
RECEIVED JANUARY 20, 1959

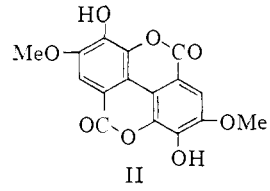
Improved procedures for the synthesis of monoalkyl-gallic acids, ellagic acid 4,4'-diacetate and the isomeric 3,3'- and 4,4'-di-O-methylellagic acids have been developed. 3,3'-Di-O-methylflavellagic acid and 3,3',4-tri-O-methyl- and tri-O-benzyl-ellagic acids were isolated as side products in some of these reactions.

Alkylated gallic and ellagic acid derivatives have become increasingly important in studies on the naturally occurring gallotannins and ellagitannins. Many of the partial methyl ethers have been prepared; however, in some cases the reactions used have not given satisfactory yields of these ethers.

(1) Financial support for this work was provided by the Diamond Walnut Growers, Inc., Stockton, Calif.

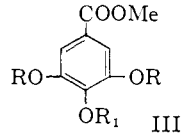
During an investigation on the constitution of ellagorubin[2] it was desired to compare the spectra of certain of its degradation products with those of the isomeric 3,3′- (I) and 4,4′-di-O-methyl (II) derivatives of ellagic acid. This opportunity was


I

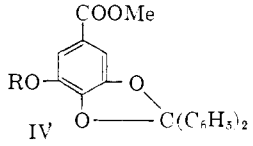

II

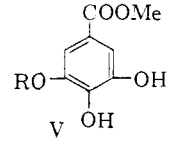
therefore taken to investigate a number of different approaches to the synthesis of I and II, although these compounds were described very recently by Schmidt[3] and Hathway,[4] respectively. Improved procedures for the synthesis of I and II and of the intermediate mono-alkyl-gallic acids thereby have been developed.

3- and 4-Monoalkyl Ethers of Gallic Acid.—Benzyl chloride reacts with equimolecular quantities of methyl gallate and potassium hydroxide to give a new mono-O-benzyl derivative, m.p. 133.5°, of methyl gallate. Since methylation followed by debenzylation of this product produces methyl syringate (III, R = Me, R_1 = H) and syringic acid, it is the 4-O-benzyl derivative (III, R = H, R_1 = $C_6H_5CH_2$–). Methyl 4-O-methylgallate is best prepared by the process of Schöpf and Winterhalder.[5]


III

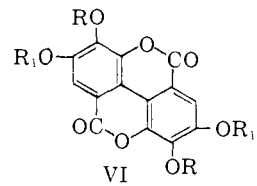
Following the work of Schmidt, Voigt, Puff and Köster[6] on the didiphenylmethylenedioxy derivative of ellagic acid it has been found that equimolecular amounts of methyl gallate and α,α-dichlorodiphenylmethane react to give a high yield of methyl 3-hydroxy-4,5-diphenylmethylenedioxybenzoate (IV, R = H) when merely heated together at 170–180° for a few minutes. This process does not form the side products obtained in the pyridine reaction of Bradley, Robinson and Schwarzenbach.[7] Compound IV, R = H, is readily methylated and benzylated in acetone solution to give IV, R = Me, and IV, R = $C_6H_5CH_2$–, respectively. Hydrolysis of the diphenylmethylene-

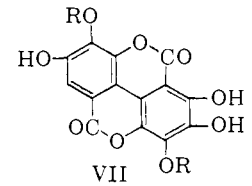

IV


V

dioxy group of IV, R = Me or $C_6H_5CH_2$–, occurs readily in dilute acetic acid *without* hydrolysis of the carbomethoxy group to give methyl 3-O-methylgallate (V, R = Me) and the new methyl 3-O-benzylgallate (V, R = $C_6H_5CH_2$), respectively. The ability to cleave the diphenylmethylenedioxy grouping without hydrolysis of an ester linkage is particularly interesting and may be useful in effecting a synthesis of such naturally occurring depsides as *m*-digallic acid. This possible route for depside synthesis is currently being explored.

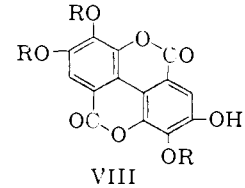
3,3′- and 4,4′-Dialkyl and 3,3′,4′-Trialkyl Ethers of Ellagic Acid.—The oxidation of gallic acid and its esters by potassium persulfate in glacial acetic acid–sulfuric acid solution gives ellagic acid[8] (VI, R = R_1 = H) whereas in sulfuric acid alone flavellagic acid[9] (VII, R = H) is formed. Oxidation of the monoalkyl ethers of gallic acid in acetic


VI


VII

acid–sulfuric acid might therefore be expected to produce di-O-alkylellagic acids. The oxidation of methyl 4-O-methylgallate in either acetic acid–sulfuric acid or in dilute aqueous sulfuric acid, however, gives the previously unknown 3,3′-di-O-methylflavellagic acid (VII, R = Me), m.p. 325°. Methyl 3-O-methylgallate, similarly oxidized, gives the desired 4,4′-di-O-methylellagic acid (II), m.p. > 360°. Crystalline products were not obtained in similar oxidation experiments on the 3-and 4-O-benzylgallic acid esters.

In the synthesis of octamethylvaloneic acid dilactone, Schmidt, Komareck and Rentél[3] converted ellagic acid tetraacetate into ellagic acid 4,4′-diacetate (VI, R = H, R_1 = CH_3CO–) by partially hydrolyzing it in a mixture of acetophenone and potassium carbonate for 6 hours. This important hydrolysis step is more easily accomplished by warming the ellagic acid tetraacetate with aqueous pyridine for a few minutes. The tetraacetate dissolves and almost immediately the pure 4,4′-diacetate crystallizes. Methylation of the 4,4′-diacetate with diazomethane as reported by Schmidt[3] gives the dimethyl ether diacetate (VI, R = Me, R_1 = CH_3CO–) which is hydrolyzed to 3,3′-di-O-methylellagic acid (I), m.p. 330–331°. Methylation of the ellagic acid 4,4′-diacetate with dimethyl sulfate and potassium carbonate in acetone gives in addition to the dimethyl ether diacetate, a small quantity of the monoacetate (m.p. 251°) of the previously unknown 3,3′,4-tri-O-methylellagic acid (VIII, R = Me), m.p. 283°.


VIII

(2) Part VII, L. Jurd, THIS JOURNAL, **81**, 4610 (1959).
(3) O. T. Schmidt, E. Komarek and H. Rentél, *Ann.*, **602**, 50 (1957).
(4) D. E. Hathway, *J. Chem. Soc.*, 519 (1957).
(5) C. Schöpf and L. Winterhalder, *Ann.*, **544**, 62 (1940).
(6) O. T. Schmidt, H. Voight, W. Puff and R. Köster, *ibid.*, **586**, 165 (1954).
(7) W. Bradley, R. Robinson and G. Schwarzenbach, *J. Chem. Soc.*, 793 (1930).
(8) A. G. Perkin and M. Nierenstein, *J. Chem. Soc., Trans. Sec.*, **87**, 1412 (1905).
(9) A. G. Perkin, *J. Chem. Soc.*, **89**, 251 (1906).

Benzylation of ellagic acid 4,4′-diacetate produces 3,3′-di-O-benzylellagic acid diacetate (VI, R = $C_6H_5CH_2$–, R_1 = CH_3CO–) together with the monoacetate (m.p. 222°) of 3,3′,4-tri-O-benzylellagic acid (VIII, R = $C_6H_5CH_2$–), m.p. 203°. This monoacetate is probably identical with that (m.p. 227–228°) isolated, but not further identified, by Schmidt and his co-workers[6] as a by-product in the preparation of tetra-O-benzylellagic acid. Hydrolysis of the 3,3′-di-O-benzylellagic acid diacetate gives 3,3′-di-O-benzylellagic acid (VI, R = $C_6H_5CH_2$–, R_1 = H) which on methylation yields VI (R = $C_6H_5CH_2$–, R_1 = Me). Analyses of each of these di-O-benzyl derivatives indicated the presence of small quantities of the corresponding tri-O-benzyl compounds. Because of the insolubility of these compounds in the usual solvents the tri-O-benzyl impurities could not be satisfactorily removed by recrystallization. The crude dimethyl ether (VI, R = $C_6H_5CH_2$–, R_1 = Me) is debenzylated in acetic anhydride–sulfuric acid solution to give VI (R = CH_3CO–, R_1 = Me), m.p. 324°, which is purified readily by crystallization from dioxane. Hydrolysis of the diacetate then gives 4,4′-di-O-methylellagic acid (II).

It is of interest to note that Shinoda and Kun[10] isolated a di-O-methylellagic acid (m.p. 337–338°; diacetate, m.p. 298–300°) from *Euphorbia formosana*. They suggested it was the 3,3′-dimethyl derivative. The similarity of the properties of the synthetic 3,3′-di-O-methylellagic acid confirms their conclusion.

Experimental

4-O-Benzylgallic Acid.—A mixture of methyl gallate (18.4 g.), potassium hydroxide (5.6 g.), benzyl chloride (19.0 g.), ethanol (50 ml.) and water (20 ml.) was refluxed for 5 hours, diluted with water and extracted with ether (3 × 100 ml.). The ether solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated. The oily residue was warmed with hexane and the mixture cooled, whereupon the oil crystallized. The crystals were warmed with benzene (100 ml.) and the undissolved methyl gallate (3.8 g.) was collected. The warm benzene filtrate was diluted with hexane (50 ml.) and cooled. The crystalline product thus obtained was extracted with hot water (3 × 100 ml.) to remove last traces of methyl gallate. The water-insoluble residue then was recrystallized from aqueous methanol. Methyl 4-O-benzylgallate was obtained as colorless needles, m.p. 133.5°, which did not give a color with alcoholic ferric chloride (4.2 g.).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.15; 1 MeO–, 11.4. Found: C, 65.7; H, 5.21; MeO–, 11.3.

Acetylation of the above ester gave methyl 4-O-benzylgallate diacetate which crystallized from benzene–hexane in colorless needles, m.p. 111°.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.7; H, 5.06; 2 CH_3CO–, 24.0. Found: C, 63.7; H, 5.04; CH_3CO–, 24.1.

Hydrolysis of the methyl 4-O-benzylgallate in cold aqueous sodium hydroxide gave 4-O-benzylgallic acid which separated from aqueous methanol in colorless needles, m.p. 170°.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.6; H, 4.65. Found: C, 64.7; H, 4.75.

Methylation of the methyl 4-O-benzylgallate (1.0 g.) by means of methyl iodide and potassium carbonate in acetone gave methyl 3,5-di-O-methyl-4-O-benzylgallate (0.9 g.) which crystallized from hexane in colorless needles, m.p. 71–72°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.00; 3 MeO–, 30.8. Found: C, 67.7; H, 6.08; MeO–, 30.8.

Hydrogenation of the above dimethyl ether (0.3 g.) in ethanol (10 ml.) in the presence of palladium–charcoal gave methyl syringate, m.p. 107° (lit.[11] m.p. 106°).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.6; H, 5.70; 3 MeO–, 43.9. Found: C, 56.9; H, 5.85; MeO–, 43.7.

Hydrolysis of the methyl 3,5-di-O-methyl-4-O-benzylgallate (0.3 g.) in glacial acetic acid (2.0 ml.) and concentrated hydrochloric acid (2.0 ml.) gave syringic acid, m.p. and mixed m.p. 204°.

Methyl 3-Hydroxy-4,5-diphenylmethylenedioxybenzoate.—A mixture of methyl gallate (20.0 g.) and α,α-dichlorodiphenylmethane (25.6 g.) was maintained at 170–180° for 5 minutes. The cooled reaction mixture was extracted with warm benzene (200 ml.) leaving a residue of unreacted methyl gallate (3.1 g.). On dilution with hexane (300 ml.) the benzene filtrate deposited a crystalline solid (29.8 g.). This was collected, washed with warm water and recrystallized from methanol. Methyl 3-hydroxy-4,5-diphenylmethylenedioxybenzoate was thus obtained in colorless prisms, m.p. 165° (lit.[7] m.p. 165°).

Anal. Calcd. for $C_{21}H_{16}O_5$: C, 72.4; H, 4.58; 1 MeO–, 8.96. Found: C, 72.4; H, 4.71; MeO–, 8.92.

Methyl 3-Methoxy-4,5-diphenylmethylenedioxybenzoate.—The above product (63.0 g.), anhydrous potassium carbonate (75.0 g.), methyl iodide (100 ml.) and acetone (400 ml.) was heated under reflux for 6 hours. The filtered acetone solution was evaporated, the residue was washed with water and recrystallized from methanol. Methyl 3-methoxy-4,5-diphenylmethylenedioxybenzoate thereby separated in colorless, brittle prisms, m.p. 135° (lit.[7] m.p. 134.5°).

Anal. Calcd. for $C_{22}H_{18}O_5$: C, 72.9; H, 5.01; 2MeO–, 17.1. Found: C, 73.0; H, 5.04; MeO–, 17.1.

Methyl 3-O-Methylgallate.—A solution of methyl 3-methoxy-4,5-diphenylmethylenedioxybenzoate (2.0 g.) in glacial acetic acid (16.0 ml.) and water (4.0 ml.) was refluxed for 7 hours. Evaporation of the solution then gave an oily residue. This was suspended in water and extracted with hexane to remove benzophenone (discarded) and with ether (3 × 20 ml.). The dried ether extract was evaporated and the residue was crystallized from benzene–hexane. Methyl 3-O-methylgallate thereby separated in colorless prisms, m.p. 112° (lit.[12] m.p. 112–113°), which gave a blue color with methanolic ferric chloride (0.72 g.). Acid hydrolysis of this product gave 3-O-methylgallic acid, m.p. 220° (lit. m.p. 220°).

Anal. Calcd. for $C_8H_8O_5$: C, 52.5; H, 4.40; 1 MeO–, 16.9. Found: C, 52.3; H, 4.40; MeO–, 16.8.

Methyl 3-Benzyloxy-4,5-diphenylmethylenedioxybenzoate.—A mixture of methyl 3-hydroxy-4,5-diphenylmethylenedioxybenzoate (30 g.), potassium iodide (6.0 g.), potassium carbonate (30 g.), benzyl chloride (20 ml.) and acetone (250 ml.) was refluxed for 5 hours. The potassium salts and precipitated solid were collected and suspended in water (600 ml.). The undissolved solid was collected, added to the original acetone filtrate and the mixture concentrated to about 150 ml. Methanol (150 ml.) was added and the mixture cooled. The crystalline product thus obtained was recrystallized from acetone–methanol. Methyl 3-benzyloxy-4,5-diphenylmethyldioxybenzoate separated in colorless prisms, m.p. 149° (35 g.).

Anal. Calcd. for $C_{28}H_{22}O_5$: C, 76.7; H, 5.06; 1 MeO–, 7.12. Found: C, 76.6; H, 5.02; MeO–, 7.09.

Methyl 3-O-Benzylgallate.—The above product (10.0 g.) was dissolved in hot glacial acetic acid (100 ml.). Water (20 ml.) was added and the mixture was heated for 6 hours. Evaporation of the reaction mixture gave an oily solid. This was washed thoroughly with hexane and recrystallized from aqueous methanol. Methyl 3-O-benzylgallate was obtained in colorless needles, m.p. 147° (5.6 g.).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.15; 1 MeO–, 11.3. Found: C, 65.8; H, 5.11; MeO–, 11.1.

The diacetate of this product, prepared by heating it with acetic anhydride and sodium acetate, crystallized from benzene–hexane in colorless needles, m.p. 104–105°.

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.7; H, 5.06. Found: C, 63.8; H, 5.01.

(10) J. Shinoda and C. P. Kun, *J. Pharm. Soc. Japan*, **51**, 502 (1930); *C. A.*, **25**, 4870 (1931).

(11) C. Graebe and E. Martz, *Chem. Ber.*, **36**, 215 (1903).

(12) F. Mauthner, *J. prakt. Chem.*, **133**, 120 (1932).

3,3'-Di-O-Methylflavellagic Acid.—Potassium persulfate (6.0 g.) was added in several portions during 5 minutes to a boiling solution of methyl 4-O-methylgallate (6.0 g.) in glacial acetic acid (60 ml.) and concentrated sulfuric acid (4.0 ml.). A yellow crystalline product separated. The mixture was heated for an additional ten minutes on the steam-bath, diluted with water and filtered. The yellow needles (1.1 g.) were recrystallized successively from aqueous pyridine and from acetone–methanol giving 3,3'-di-O-methylflavellagic acid, m.p. 325–326° dec.

Anal. Calcd. for $C_{16}H_{10}O_9$: C, 55.5; H, 3.12; 2 MeO–, 17.9. Found: C, 55.6; H, 3.01; MeO–, 17.8.

The triacetate of this product, prepared by heating it with acetic anhydride and sodium acetate, separated from acetone–methanol in colorless needles, m.p. 244°.

Anal. Calcd. for $C_{22}H_{16}O_{12}$: C, 55.9; H, 3.42; 2 MeO–, 13.1. Found: C, 56.1; H, 3.42; MeO–, 12.9.

Methylation of above oxidation product with dimethyl sulfate, potassium carbonate and acetone gave the known penta-O-methylflavellagic acid, m.p. 244–245° (lit.[13] m.p. 242°).

Oxidation of methyl-4-O-methylgallate (1.0 g.) in water (10 ml.) and sulfuric acid (0.5 ml.) with potassium persulfate (1.0 g.) for an hour gave 3,3'-di-O-methylflavellagic acid, m.p. 325° (triacetate, m.p. 244°) (0.13 g.).

Ellagic Acid 4,4'-Diacetate.—A suspension of ellagic acid tetraacetate (2.0 g.) in pyridine (10.0 ml.) was heated to boiling. Water (5.0 ml.) was added, the mixture was heated briefly to boiling and then on a steam-bath for 3 minutes. The ellagic acid tetraacetate dissolved to give a yellow solution. Almost immediately yellow needles began to separate. Water (30 ml.) was added, the mixture was cooled and the crystalline product was collected. After washing with water, methanol and acetone the product was recrystallized from N,N-dimethylformamide. Ellagic acid 4,4'-diacetate (1.3 g.) separated in almost colorless needles, m.p. 325–327° (lit.[3] m.p. 350°) which did not give a color with methanolic ferric chloride.

Anal. Calcd. for $C_{18}H_{10}O_{10}$: C, 55.9; H, 2.80; 2 CH_3CO–, 22.3. Found: C, 55.8; H, 2.69; CH_3CO–, 22.2.

3,3'-Di-O-Methyl- and 3,3',4-Tri-O-Methylellagic Acid.—(a) A suspension of ellagic acid 4,4'-diacetate (0.3 g.) in acetone was treated with excess of ethereal diazomethane for 3 hours. Evaporation of the mixture gave a crystalline residue which was recrystallized from dioxane–methanol. 3,3'-Di-O-methylellagic acid 4,4'-diacetate thereby separated in colorless needles, m.p. 304–305 (lit.[3] m.p. 302–305°).

Anal. Calcd. for $C_{20}H_{14}O_{10}$: C, 57.95; H, 3.41; 2 MeO–, 15.0. Found: C, 58.0; H, 3.44; MeO–, 15.1.

(b) A mixture of ellagic acid 4,4'-diacetate (10.0 g.) anhydrous potassium carbonate (15.0 g.), dimethyl sulfate (20.0 ml.) and anhydrous acetone (200 ml.) was heated under reflux for 3 hours. The precipitated solid and potassium salts were filtered (A). The acetone filtrate was concentrated and diluted with methanol whereupon colorless needles (0.7 g.) separated. Recrystallized from dioxane–methanol, this product, 3,3',4-tri-O-methylellagic acid monoacetate, separated in colorless needles, m.p. 251°.

Anal. Calcd. for $C_{19}H_{14}O_9$: C, 59.0; H, 3.66; 3 MeO–, 24.1; 1 CH_3CO–, 11.2. Found: C, 59.3; H, 3.72; MeO–, 24.6; CH_3CO–, 11.2.

A suspension of the above monoacetate (0.2 g.) in acetone (5.0 ml.) and methanol (5.0 ml.) was heated to boiling and treated with 10% aqueous sodium hydroxide (3.0 ml.). After 3 minutes water (20 ml.) was added and heating was continued for 10 minutes. The yellow solution was acidified and filtered. The solid thus obtained was recrystallized from acetone–methanol and from tetrahydrofuran–methanol. 3,3',4-Tri-O-methylellagic acid separated in slightly yellow needles, m.p. 283°.

Anal. Calcd. for $C_{17}H_{12}O_8$: C, 59.3; H, 3.51; 3 MeO–, 27.05. Found: C, 59.3; H, 3.62; MeO–, 27.1.

The acetone-insoluble solid (A) was suspended in water (400 ml.). The undissolved solid was collected and recrystallized from dioxane–methanol. 3,3'-Di-O-methylellagic acid 4,4'-diacetate was thus obtained as colorless needles, m.p. 304–305° (6.6 g.).

Aqueous sodium hydroxide (40.0 ml., 10%) was added to a suspension of 3,3'-di-O-methylellagic acid 4,4'-diacetate (6.5 g.) in acetone (60 ml.) and methanol (100 ml.). The mixture was heated on a steam-bath for 5 minutes, diluted with water (400 ml.) and filtered. The filtrate was acidified with concentrated hydrochloric acid and digested on a steam-bath for 10 minutes. The precipitated solid was collected and recrystallized from aqueous pyridine and from dioxane–methanol. 3,3'-Di-O-methylellagic acid (4.8 g.) thereby separated in slightly yellow needles, m.p. 330–331° (lit.[3] m.p. 319–320°).

Anal. Calcd. for $C_{16}H_{10}O_8$: C, 58.2; H, 3.27; 2 MeO–, 18.8. Found: C, 58.2; H, 3.14; MeO–, 18.6.

Benzylation of the 3,3'-di-O-methylellagic acid gave 3,3'-di-O-methyl-4,4'-di-O-benzylellagic acid, m.p. 292° (lit.[3] m.p. 295–296°).

Anal. Calcd. for $C_{30}H_{22}O_8$: C, 70.55; H, 4.35; 2 MeO–, 12.2. Found: C, 70.7; H, 4.43; MeO–, 12.2.

4,4'-Di-O-Methylellagic Acid.—(a) A solution of methyl 3-O-methylgallate (5.5 g.), potassium persulfate (5.5 g.) and concentrated sulfuric acid (2.0 ml.) in water (40 ml.) was heated on a steam-bath for one hour, cooled and filtered. The gummy, highly colored solid thus obtained was washed successively with warm water and warm acetone. 4,4'-Di-O-methylellagic acid remained as a slightly brown, crystalline powder, m.p. >360° (0.65 g.). It was converted into its diacetate by boiling with acetic anhydride and sodium acetate for 30 minutes. Crystallized from dioxane–methanol, 4,4'-di-O-methylellagic acid diacetate was obtained in colorless needles, m.p. 324° (lit.[4] m.p. 320°).

Anal. Calcd. for $C_{20}H_{14}O_{10}$: C, 57.95; H, 3.41; 2 MeO–, 15.0; 2 CH_3CO–, 20.8. Found: C, 58.2; H, 3.48; MeO–, 14.8; CH_3CO–, 21.3.

(b) A mixture of ellagic acid 4,4'-diacetate (2.6 g.), potassium iodide (5.0 g.), anhydrous potassium carbonate (5.0 g.), benzyl chloride (5.0 ml.) and dry acetone (60 ml.) was refluxed for 48 hours. The precipitated solid and potassium salts were filtered (A). The acetone filtrate was evaporated to an oil which was suspended in hexane (100 ml.). A crystalline solid was thereby precipitated. It was collected and recrystallized successively from acetone–methanol and from benzene–hexane. 3,3',4-Tri-O-benzylellagic acid monoacetate was thus obtained as colorless needles, m.p. 222° (0.32 g.).

Anal. Calcd. for $C_{37}H_{26}O_9$: C, 72.3; H, 4.27; 1 CH_3CO–, 7.0. Found: C, 72.2; H, 4.33; CH_3CO–, 7.6.

The monoacetate (0.2 g.) was heated on a steam-bath for 5 minutes with acetone (30 ml.), ethanol (20 ml.) and 10% aqueous sodium hydroxide (10.0 ml.). Water (100 ml.) was added and the solution was acidified with hydrochloric acid. The acid solution was heated for 30 minutes. The crystalline precipitate then was collected and recrystallized from acetone–methanol. 3,3',4-Tri-O-benzylellagic acid separated in slightly yellow needles, m.p. 203°, which did not give a color with alcoholic ferric chloride.

Anal. Calcd. for $C_{35}H_{24}O_8$: C, 73.4; H, 4.23. Found: C, 73.4; H, 4.31.

The acetone-insoluble solid (A) was suspended in water (100 ml.) and the undissolved white solid was collected, washed with acetone and dried (2.1 g., m.p. 282–283°). Recrystallized from N,N-dimethylformamide containing some methanol 3,3'-di-O-benzylellagic acid diacetate separated in colorless felted needles, m.p. 291°. This product was contaminated with the tri-O-benzylellagic acid monoacetate.

Anal. Calcd. for $C_{32}H_{22}O_{10}$: C, 67.8; H, 3.92; 2 CH_3CO–, 15.2. Found: C, 69.4; H, 4.08; CH_3CO–, 12.6.

The crude diacetate (1.6 g.) was heated with methanol (50 ml.), acetone (50 ml.) and 10% aqueous sodium hydroxide (20 ml.) for 5 minutes. Water (200 ml.) was added and the solution was acidified (HCl). The yellow solid was collected and recrystallized from acetone–methanol. The crude 3,3'-di-O-benzylellagic acid separated in yellow needles (1.1 g.), m.p. 235–240°. The whole of this product was methylated by refluxing it with dimethyl sulfate (5.0 ml.), potassium carbonate (4.0 g.) and acetone (40 ml.) for 6 hours. The acetone-insoluble product was collected and suspended in water. The undissolved dimethyl ether was collected and recrystallized from glacial acetic acid. 4,4'-

(13) I. Heilbron and H. M. Bunbury, Eds., "Dictionary of Organic Compounds," Oxford University Press, N. Y., 1953, Vol. II, p. 541.

Di-O-methyl-3,3′-di-O-benzylellagic acid separated in colorless needles, m.p. 239–241°.

Anal. Calcd. for $C_{30}H_{22}O_8$: C, 70.5; H, 4.35; 2 MeO–, 12.2. Found: C, 71.8; H, 4.45; MeO–, 10.0.

The crude di-O-methyl-di-O-benzylellagic acid (0.7 g.) was suspended in acetic anhydride (20.0 ml.). Concentrated sulfuric acid (1.0 ml.) was added and the solution was heated on a steam-bath for 2 hours. It was allowed to stand at room temperature for 24 hours, diluted with water and filtered. The solid thus obtained was washed with acetone and recrystallized from dioxane–methanol. 4,4′-Di-O-methylellagic acid diacetate thus was obtained in colorless needles, m.p. 324° (0.4 g.).

Anal. Calcd. for $C_{20}H_{14}O_{10}$: C, 57.95; H, 3.41; 2 MeO–, 15.0; 2 CH_3CO–, 20.8. Found: C, 58.1; H, 3.42; MeO–, 14.7; CH_3CO–, 21.6.

The diacetate was hydrolyzed by heating it with dioxane (10.0 ml.), methanol (10 ml.) and 10% aqueous sodium hydroxide (5.0 ml.) for 10 minutes. After dilution with water and acidification the solid product was collected and recrystallized from a large volume of N,N-dimethylformamide. 4,4′-Di-O-methylellagic acid was thereby obtained in colorless needles, m.p. >360° (lit.[4] m.p. > 320°).

Anal. Calcd. for $C_{16}H_{10}O_8$: C, 58.2; H, 3.27; 2 MeO–, 18.8. Found: C, 58.0; H, 3.22; MeO–, 18.2.

Acknowledgment.—The author is indebted to L. M. White for performing the elementary analyses.

PASADENA, CALIF.

[CONTRIBUTED FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, A LABORATORY OF THE WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

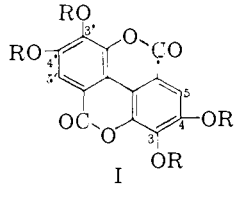
Plant Polyphenols. VII. The Structure of Ellagorubin[1]

BY LEONARD JURD

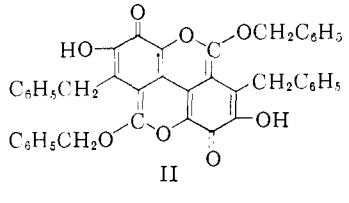
RECEIVED JANUARY 20, 1959

Hydrolysis of di-O-methylellagorubin gives a di-O-methyl-5,5′-di-C-benzylellagic acid (A). Hydrolysis of di-O-benzylellagorubin forms the corresponding di-O-benzyl-5,5′-di-C-benzylellagic acid. Methylation and subsequent debenzylation of this gives a di-O-methyl-5,5′-di-C-benzylellagic acid (B). Comparison of the ultraviolet spectra of these ethers, (A) and (B), with the spectra of synthetic 3,3′-di-O-methylellagic acid (IV) and 4,4′-di-O-methylellagic acid (V) establishes the constitution of (A) as 3,3′-di-O-methyl-5,5′-di-C-benzylellagic acid (X) and of (B) as 4,4′-di-O-methyl-5,5′-di-C-benzylellagic acid (XI). From these data it follows that ellagorubin has the structure XII and not II as previously reported.

The widespread distribution of ellagic acid derivatives in the plant kingdom[2–4] has resulted in a considerable current interest in the chemistry of this acid.[5–7] The extensive investigations of Schmidt and his co-workers at Heidelberg are particularly significant.[8] Ellagic acid is a polyphenolic dilactone (I, R = H) which reacts normally with benzyl chloride in acetophenone to give the colorless tetra-O-benzyl derivative (I, R = $C_6H_5CH_2$–).[9] In aqueous alkali, however, Schmidt, Voigt and Bernauer[10] found that ellagic acid and benzyl chloride react to form a deep red pigment, ellagorubin, for which they proposed the quinoidal structure II.

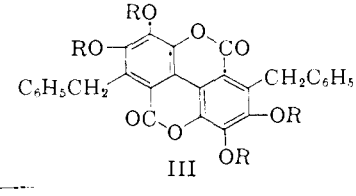


I



II

Because of the novel nature of this benzylation product, Schmidt's work has been extended in this Laboratory. It already has been reported[11] that, although the benzylation of ellagic acid gives ellagorubin under the conditions described by Schmidt, the presence of small amounts of pyridine inhibits the formation of ellagorubin and produces the colorless compound, 5,5′-di-C-benzyl-tetra-O-benzylellagic acid (III, R = $C_6H_5CH_2$–), together with a small quantity of a yellow pigment which is partially quinoidal and partially aromatic. In the process of identifying the ellagorubin formed in these reactions its dimethyl ether was hydrolyzed to the di-O-methyl-5,5′-di-C-benzylellagic acid described by Schmidt and his co-workers as the 4,4′-di-O-methyl derivative XI. The ultraviolet spectra of this dimethylellagic acid derivative in various media, however, could not be satisfactorily accounted for on the basis of the orientation of methoxyl and hydroxyl groups suggested by these authors. The reactions of ellagorubin have therefore been re-examined. In this paper chemical evidence and ultraviolet spectral data are presented which establish structure XII for ellagorubin. In the following paper[12] structure XII, but not structure II, is shown to be compatible with infrared and nuclear magnetic resonance spectral data.



III

(1) Financial support for this work was provided by the Diamond Walnut Growers, Inc.

(2) A. G. Perkin and M. Nierenstein, *J. Chem. Soc. (Trans.)*, **87**, 1412 (1905).

(3) E. C. Bate-Smith, *Chemistry & Industry*, R 32 (1956).

(4) O. T. Schmidt and W. Mayer, *Angew. Chem.*, **68**, 103 (1956).

(5) D. E. Hathway, *Nature*, **177**, 747 (1956).

(6) D. E. Hathway, *Biochem. J.*, **67**, 445 (1957).

(7) D. E. Hathway, *J. Chem. Soc.*, 519 (1957).

(8) O. T. Schmidt, E. Komarek and H. Rentél, *Ann.*, **602**, 50 (1957), and previous papers in this series.

(9) O. T. Schmidt, H. Voigt, W. Puff and R. Köster, *ibid.*, **586**, 165 (1954).

(10) O. T. Schmidt, H. Voigt and K. Bernauer, *Chem. Ber.*, **88**, 91 (1955).

(11) Part II, L. Jurd, THIS JOURNAL, **79**, 6043 (1957).

(12) Part VIII, F. Stitt, E. Gong, K. J. Palmer and J. N. Shoolery, *ibid.*, **81**, 4615 (1959).