

634. Trigallic Acid, A Probable Component of Tannic Acid.

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A component of tannic acid is believed to be *m*-trigallic acid. Its isolation and properties are described, and an apparently identical product is synthesised.

"TANNIC ACID" is a mixture,¹ three of whose main components are acidic and can be separated from the classical gallotannin by extraction with solvent from a neutralised solution of "tannic acid."² Two of the acidic components are gallic and *m*-digallic acid and it was suggested that the third was a trigallic acid (*a*) by reason of its position on paper chromatograms and (*b*) since brief acid hydrolysis of purified gallotannin produced gallic acid, *m*-digallic acid, and component 3. Prolonged hydrolysis destroyed component 3 and *m*-digallic acid in that order, the sole product from each being then gallic acid.

Component 3 has since been isolated by chromatographing the mixture of acids on a column of "Solka Floc" powdered cellulose. For comparison, a synthetic trigallic acid was made by condensing penta-*O*-acetyl-*p*-digalloyl chloride with 3,5-di-*O*-acetylgallic acid, then simultaneously deacetylating and rearranging the resulting hepta-acetyl derivative.

The synthetic and the natural product each crystallise from water with two molecules of water of crystallisation. They appear to have identical paper chromatographic and ultraviolet spectrophotometric properties, and elementary analyses are satisfactory, but the synthetic sample has a lower melting point although the mixed melting point is intermediate. Total acid hydrolysis of both acids produced gallic acid in about the expected molecular ratio, as found by measurements of ultraviolet spectra;³ molecular-weight and equivalent-weight determinations for the synthetic product gave values of the right order.

Both the synthetic and the natural product are believed to be *m*-trigallic acids since alkaline hydrolysis of the methylation product yielded only 3,4-di- and 3,4,5-tri-*O*-methylgallic acid. The initial methylations were intended to produce the methyl ester of fully methylated trigallic acid but in each case the product had too high a methoxyl content. Independent work on corresponding structures at the University of Sheffield⁴ suggests that methylation with diazomethane caused methanolysis of the parent acids, yielding mixtures of methyl tri- and di-*O*-methylgallate.

Determination of the *ortho*-hydroxyl value of the synthetic acid by the ferrous tartrate method³ supported the formulation as a *m*-galloyl-*m*-digallic acid. The compound behaved as a galloyl ester, giving a value of 68.6% of pyrogalloyl-type groups (calc. 72.2%).

Neither the occurrence nor the synthesis of a *m*-galloyl-*m*-digallic acid has been reported previously. Fischer and Freudenberg⁵ synthesised a trigallic acid by treating tri-*O*-methoxygalloyl chloride with gallic acid, but gave it the structure 3,5-digalloylgallic acid. The demonstration of the presence of a trigallic acid residue in the gallotannin molecule is, of course, of some importance.

EXPERIMENTAL

Synthesis of Trigallic Acid.—*Hepta-O-acetyltrigallic acid.* Penta-*O*-acetyl-*p*-digallic acid (7.5 g.) was made into a slurry in carbon tetrachloride (22.5 ml.), and phosphorus pentachloride (7.5 g.) was added in small portions. The mixture was warmed on a water-bath until dissolution took place. The excess of pentachloride was removed by filtration through glass wool.

¹ White, Kirby, and Knowles, *J. Soc. Leather Trades' Chemists*, 1952, **36**, 148.

² King, Ph.D. Thesis, London, 1957.

³ King and White, "Symposium on Chemistry of Vegetable Tannins," Society of Leather Trades' Chemists, Croydon, 1956.

⁴ Professor R. D. Haworth, personal communication.

⁵ Fischer and Freudenberg, *Ber.*, 1912, **45**, 2709.

The acid chloride crystallised overnight at 0°. The cream-coloured product, re-crystallised from carbon tetrachloride, had m. p. 150° (3.5 g., dried at 76° over P₂O₅ in a vacuum).

3,5-Di-*O*-acetylgallic acid (1.75 g.) in acetone (10 ml.) was cooled to -5° with stirring and aqueous *N*-sodium hydroxide (6.5 ml.) was added. Penta-*O*-acetyl-*p*-galloyl chloride (3.5 g.) in acetone (3 ml.) was added with simultaneous additions of *N*-sodium hydroxide (1.3 ml.). The purple solution formed was acidified to Congo Red with dilute hydrochloric acid, yielding a brown oil. Water (25 ml.) was added and the oil rubbed until it solidified. The cream-coloured plastic product had m. p. 142° (decomp.) (3.6 g., dried at 100° over P₂O₅ in a vacuum).

Trigallic acid. To a slurry of hepta-*O*-acetyltrigallic acid (2.5 g.) in water (10 ml.) at -5° under hydrogen, 5*N*-ammonia was added dropwise until the solid dissolved. The pink solution was kept for 1 hr. at room temperature, then acidified to Congo Red paper and kept at 0° overnight. The white precipitate of *trigallic acid* was filtered off, washed with chloroform, allowed to dry, and washed again with cold water (yield, 1.39 g., dried at 100° as above), then having m. p. 213° (decomp.) after softening at 170°. The product was recrystallised from water, giving an acid showing no other components on two-way paper chromatography [*R_F* 0.13 in 6% acetic acid, 0.81 in butan-2-ol-acetic acid-water (14 : 1 : 5)] and having m. p. 217° (decomp.) after softening at 192° (Found: C, 49.2; H, 3.5; loss in wt. at 140°/0.1 mm., 6.7. Calc. for C₂₁H₁₄O₁₃·2H₂O: C, 49.3; H, 3.5; H₂O, 7.6%).

The ultraviolet spectrum of the product in ethanol showed a single maximum at 270 mμ (*E*_{1%¹cm.} 598), minimum at 240 mμ (*E*_{1%¹cm.} 263). Hydrolysis by 2*N*-sulphuric acid (2 ml.) of this material (2.52 mg.) was carried out for 16 hr. at 100°. The volume of solution was made up to 100 ml. with water. Two-dimensional paper chromatography of the solution showed the presence of a single component, gallic acid, whose ultraviolet spectrum showed a maximum at 270 mμ (*E*_{1%¹cm.} 570). The corresponding *E*_{1%¹cm.} value for gallic acid treated as above was 552 at the same wavelength.³

The *ortho*-di- and tri-hydroxyl content of trigallic acid³ was determined by the ferrous tartrate method as follows: Trigallic acid (26.85 mg.) was dissolved in a mixture of ethanol (5 ml.) and water (45 ml.), and 10 ml. aliquot parts were developed with the buffered ferrous tartrate reagent, measurements being made at 545 mμ. The *E* value between borate and acetate buffer readings was negligible, indicating that the compound was behaving as a galloyl ester (*m*-digallic acid type). The analytical result was 68.6% of pyrogallol-type groups (calc. for a 4,4'-digalloylgallic acid, 26.5%; for a 3,5'-digalloylgallic acid, 52.8%; for a 3,3'-digalloylgallic acid, 72.2%).

Molecular weight determinations were carried out for acetone solutions by the ebullioscopic method of Bobranski and Sucharda, checked against *m*-digallic acid. These gave: *m*-digallic, *M* 320 (calc., 328); trigallic acid, *M* 483, 498 (calc., 474).

Equivalent-weight determinations were carried out by potentiometric titration in 1 : 1 ethylene glycol-butan-1-ol with 0.161*N*-potassium hydroxide in the same solvent mixture. Determinations on gallic and *m*-digallic acids were used as control. Results are of the order expected if the product is made up of 3 galloyl residues, namely: gallic (hydrate), 188 (calc., 185); *m*-digallic, 322 (calc., 343); trigallic acid, 474 (calc., 441).

Methylation of trigallic acid. Trigallic acid (0.53 g.) was treated in methanol (5 ml.) and ether (25 ml.) with an excess of ethereal diazomethane, then kept at room temperature for 3 days, after which the solvent was distilled off. The residual syrup was heated with 50% aqueous methanol (10 ml.) and the irregular shaped crystals which separated on cooling were filtered off (0.46 g., dried at room temperature over P₂O₅ in a vacuum). Recrystallisation from methanol gave a derivative, m. p. 100° (the product required several days to solidify, first separating as an oil) [Found: C, 58.8; H, 5.1; OMe, 54.0. Calc. for C₂₁H₆O₅(OMe)₈: C, 59.5; H, 5.1; OMe, 42.3%]. The high methoxyl content suggests that the product is a mixture of methyl tri- and di-*O*-methylgallic acid found in the next experiment and produced by methanolysis of the parent substance.

Alkaline hydrolysis of the product of methylating trigallic acid. The methylation product (0.32 g.) was kept in methanol (10 ml.) and 10% aqueous sodium hydroxide (5 ml.) for 6 hr. at 40° in an atmosphere of nitrogen, then at room temperature overnight, and was acidified with 6*N*-hydrochloric acid. The methanol was partly distilled off and the crystalline product (crop 1) was filtered off and dried over P₂O₅ (vacuum) (yield, 0.09 g.; m. p. 145–150°). The mother-liquors were concentrated to 15 ml., further crystals being obtained (0.06 g., dried as above; m. p. 168–183°) (crop 2). Crop 2 was washed with 1 : 1 chloroform-carbon tetrachloride

(4 ml.), leaving 3,4-di-*O*-methylgallic acid which, recrystallised from water, had m. p. and mixed m. p. 187°.

The chloroform-carbon tetrachloride-soluble portion was mixed with crop 1 (soluble in the mixture), and the solvents were allowed to evaporate. The residue recrystallised from water, giving needles of 3,4,5-tri-*O*-methylgallic acid, m. p. and mixed m. p. 163°.

These results were confirmed by repeating the hydrolysis and chromatographing the acidified hydrolysate one-way on paper with butan-1-ol saturated with aqueous formic acid as solvent. Both the di- and the tri-*O*-methylgallic acid were located by a faint violet fluorescence when exposed to ammonia vapour and ultraviolet light, and by their faint yellow reactions when the chromatograms were sprayed with bisdiazotised benzidine. R_F values were: 3,4,5-tri-*O*-methylgallic acid, 0.84; 3,4-di-*O*-methylgallic acid, 0.77. Both acids reacted positively to the Bromophenol Blue indicator spray. There was no sign of 3,5-di-*O*-methylgallic or 4-*O*-methylgallic acid on these chromatograms.

Acetyl derivative of trigallic acid. Trigallic acid (100 mg.) was kept in pyridine (10.5 ml.) with acetic anhydride (5 ml.) for 2 days at room temperature, and then poured into water (50 ml.) containing 10% w/v sulphuric acid (1 ml.). The sticky product was allowed to harden and was then filtered off (136 mg., dried at 76° as above). The derivative recrystallised from dilute acetic acid, giving a *product*, m. p. 175°, softening at 125–130° [Found: C, 54.1; H, 3.7; OAc, 39.6. Calc. for $C_{21}H_{14}O_8(OAc)_7$: C, 54.8; H, 3.6; OAc = 39.3%].

Preparation of Component 3 from Tannic Acid.—Tannic acid (80 g.) was dissolved in water (400 ml.), and the solution adjusted to pH 6.5 with sodium hydrogen carbonate (about 20 g.) and then extracted with ethyl acetate (2×150 ml.; 4×100 ml.). The combined extracts were dried (Na_2SO_4) and taken to dryness (yield, 44.2 g., mainly gallotannin). Dilute hydrochloric acid was added to the aqueous residue, to give pH 2, and the solution was extracted exhaustively with ether. The extract was dried and taken to dryness, giving material (20.2 g.), predominantly a mixture of gallic and *m*-digallic acid and component 3, with a little gallotannin. The extract was dissolved in hot water (40 ml.) and allowed to cool. A white precipitate separated; this was recrystallised from water (40 ml.) (yield, 6.4 g., air-dry; mainly *m*-digallic acid with a little gallic acid and component 3). The mother-liquors were combined and taken to dryness (13 g.), the residue was dissolved in water (150 ml.), and the solution adjusted to pH 6.5 and again extracted with ethyl acetate to remove gallotannin. The aqueous residue was re-adjusted to pH 2 and extracted exhaustively with ether, the extract yielding gallic acid, *m*-digallic acid, and component 3 uncontaminated with gallotannin.

The acidic fraction (1 g.) was dissolved in the minimum amount of 5% acetic acid and applied to a "Solka Floc" column (47×3.5 cm.), the column being developed with 5% acetic acid. Samples (10 ml.) were collected as soon as the effluent reacted with the ferric chloride-potassium ferricyanide reagent, the type of acid present in each sample being checked by one-way paper chromatography (6% acetic acid). Fractions 1–12 contained gallic acid and fractions 13–57 *m*-digallic acid. The latter fractions were reduced to a small volume with repeated additions of water to remove acetic acid. *m*-Digallic acid (0.4 g.), m. p. 254°, crystallised. When paper-chromatographic checks showed that only component 3 was emerging, 24×10 ml. and 4×50 ml. samples were collected. The effluent reacted only very faintly with the ferricyanide reagent when the last sample had been collected. The fractions were combined and their volumes reduced by vacuum-distillation as before at a water-bath temperature of 50°. When the volume had been reduced to 10 ml. the precipitated component 3 was filtered off, washed with water, and dried at 75° as before [75 mg.; m. p. 226° (decomp.)]. Recrystallisation of component 3 from water raised the m. p. to 237° (decomp.), mixed m. p. with synthetic trigallic acid 222° (decomp.) (Found: C, 49.2; H, 3.5; loss in wt., 7.1. Calc. for $C_{21}H_{14}O_{13} \cdot 2H_2O$: C, 49.3; H, 3.5; H_2O , 7.6%). Hydrolysis by 2*N*-sulphuric acid (2 ml.) of component 3 (2.95 mg.) gave gallic acid as the sole product, $E_{1\text{cm}}^{1\%}$ 545 at 270 μ .³ Its behaviour on paper chromatograms was identical with that of the synthetic trigallic acid.

Methylation. Component 3 (50 mg.) was dissolved in the minimum amount of methanol, and ether (20 ml.) was added. Excess of ethereal diazomethane solution was added and the solution left at room temperature overnight. The ether was distilled off and the remaining methanolic residue was kept at 0° until crystallisation occurred. The product (40 mg., dried at room temperature as above) had m. p. 112° [Found: C, 59.1; H, 4.8. Calc. for $C_{21}H_6O_5(OMe)_8$: C, 59.5; H, 5.1%]. Methoxyl values were too high, as already explained.

Acetate. Component 3 (100 mg.) was warmed with pyridine (0.5 ml.) and acetic anhydride

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(5 ml.) until dissolved. The solution was left overnight at room temperature and, after filtration, was poured into 3·7% hydrochloric acid (50 ml.). After solidification, the acetyl derivative was filtered off and dried at room temperature over P_2O_5 in a vacuum; it (110 mg.) had m. p. 175° after softening at 125—130°, mixed m. p. with synthetic hepta-acetyltrigallic acid, 175°, softening at 125—130° [Found: C, 53·5; H, 4·0; OAc, 38·0. Calc. for $C_{21}H_7O_6(OAc)_7$: C, 54·8; H, 3·6; OAc, 39·3%].

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