407. *Gallotannins. Part VIII.* The Preparation and Properties of Some Galloyl Esters of Quinic Acid.*

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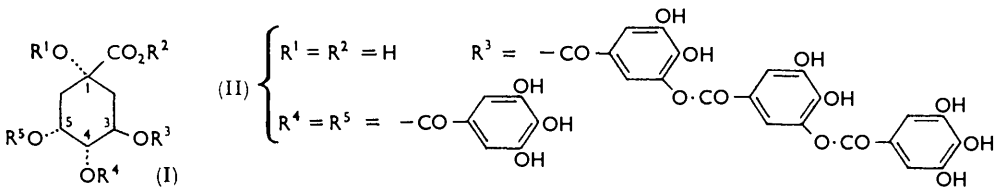
The four isomeric mono-*O*-galloylquinic acids have been synthesised and their properties described. The structure of the " core " of Tara gallotannin, as 3,4,5-tri-*O*-galloylquinic acid, has been confirmed by synthesis and, in addition, the preparation of 4,5-*O*- and 1,3,4,5-tetra-*O*-galloylquinic acid is reported.

QUINIC ACID (I; all R's = H) is widely distributed in the plant kingdom in the free state, and also commonly occurring [1,2] in plant tissues are chlorogenic acid, the 3-caffeoyl (3,4-dihydroxycinnamoyl) ester, and the corresponding 3-*p*-coumaroyl (4-hydroxycinnamoyl) ester. Recently claims [3] have been made for the existence in Nature of several isomeric esters of caffeic acid and quinic acid, such as iso- [4] and neo-chlorogenic acid,[5] but the structures of these are not known with certainty. Quinic acid has in addition been isolated from natural sources in combination with gallic acid; thus Roberts and Myers [6] obtained the amorphous theogallin from green tea and assigned to it, mainly by analogy with chlorogenic acid, the structure of 3-*O*-galloylquinic acid, and Haworth and his co-workers [7,8] have shown the acidic Tara tannin from the fruit pods of *Caesalpinia spinosa* to have the average composition of a penta-*O*-galloylquinic acid and suggested structure (II) for this substance. Parallel with the degradative work on Tara gallotannin the synthesis of several reference compounds and breakdown products of the tannin was undertaken and in this paper are described the preparation and properties of the four mono-galloyl derivatives of quinic acid, 4,5-di-, 1,3,4,5-tetra-, and 3,4,5-tri-*O*-galloylquinic acid (the " core " of the gallotannin, derived from it by methanolysis [8]).



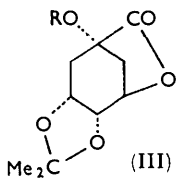
Standard procedures were used for the synthesis of 1- and 3-*O*-galloylquinic acid. Condensation of tri-*O*-benzylgalloyl chloride [9] with 4,5-*O*-isopropylidenequinide [10] (III; R = H) gave the tri-*O*-benzylgalloyl ester which on treatment with acetic acid afforded 1-*O*-(tri-*O*-benzylgalloyl)quinide (IV; $R^4 = R^5 = H$, R^1 = tri-*O*-benzylgalloyl); the latter, on hydrogenation over palladium–charcoal, gave crystalline 1-*O*-galloylquinide (IV; $R^4 = R^5 = H$, R^1 = 3,4,5-trihydroxybenzoyl) which also resulted from the action of acetic acid on 1-*O*-galloyl-4,5-*O*-isopropylidenequinide (III; R = 3,4,5-trihydroxybenzoyl) prepared by hydrogenolysis of the ester (III; R = tri-*O*-benzylgalloyl). The lactone ring of 1-*O*-galloylquinide was readily severed by the action of water at 100°, to give 1-*O*-galloylquinic acid as an amorphous solid which was characterised by its analysis

* Part VII, *J.*, 1962, 3814.

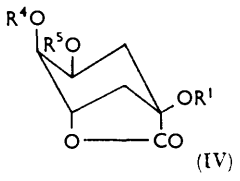
[1] Herrmann, *Naturwiss.*, 1956, **43**, 109.
[2] Haslam, Haworth, and Makinson, *J.*, 1961, 5153.
[3] Plant Phenolics Group Symposium, " Chlorogenic Acids in Plant Materials," *Chem. and Ind.*, 1958, 213.
[4] Barnes, Feldman, and White, *J. Amer. Chem. Soc.*, 1950, **72**, 4178.
[5] Corse, *Nature*, 1953, **172**, 771.
[6] Roberts and Myers, *J. Sci. Food Agric.*, 1958, **11**, 701.
[7] Armitage, Bayliss, Gramshaw, Haslam, Haworth, Jones, Rogers, and Searle, *J.*, 1961, 1842.
[8] Haslam, Haworth, and Keen, *J.*, 1962, 3814.
[9] Clinton and Geissmann, *J. Amer. Chem. Soc.*, 1943, **65**, 85.
[10] Fischer, *Ber.*, 1921, **54**, 775.

and optical rotation and by its ready conversion in warm acetic acid into 1-*O*-galloylquinide.

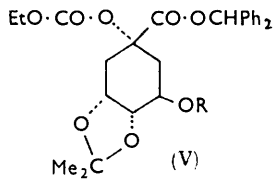
An interesting reaction was observed when 4,5-*O*-isopropylidene-1-*O*-(tri-*O*-benzylgalloyl)quinide (III; R = tri-*O*-benzylgalloyl) was treated with ethanolic barium hydroxide and the product was hydrogenated and treated with acid to remove the isopropylidene group. Paper chromatography of the residue did not show the expected 1-*O*-galloylquinic acid, but gallic acid and ethyl gallate were thus identified and they were later isolated by countercurrent distribution along with the crystalline major product of reaction. This compound showed a single carbonyl stretching frequency at 1727 cm.$^{-1}$, was extractable from neutral buffer solution (pH 6·8), and on acid hydrolysis gave gallic and quinic acid. On the basis of this and analytical evidence the compound was formulated as ethyl 1-*O*-galloylquinate (I; R^1 = 3,4,5-trihydroxybenzoyl, R^2 = Et, R^3 = R^4 = R^5 = H) which, it is suggested, arises by initial ethanolysis of the lactone ring. Hydrolysis of the ester (III; R = tri-*O*-benzylgalloyl) by barium hydroxide in dioxan with subsequent hydrogenation and acid hydrolysis gave a mixture which paper chromatography showed to contain gallic acid and 1-*O*-galloylquinide (both isolated and characterised after countercurrent distribution), 1-*O*-galloylquinic acid, and a substance identified by comparison with synthetic 3-*O*-galloylquinic acid (I; R^1 = R^2 = R^4 = R^5 = H, R^3 = 3,4,5-trihydroxybenzoyl). Qualitative experiments established that a galloyl group migrated readily from the 1- to the 3-position of quinic acid in sodium hydrogen carbonate solution, and this isomerisation and the formation of methyl or ethyl gallate when the lactone ring of the quinide ester (III; R = tri-*O*-benzylgalloyl) was severed in methanol or ethanol are readily explicable on the basis of a neighbouring-group participation involving the 1-carboxylate group, as will be discussed in detail in a later paper. The poor yields of 1-*O*-acyl derivatives of quinic acid obtained in earlier work [11,12] were probably due to the occurrence of similar rapid side reactions.



(III)



(IV)



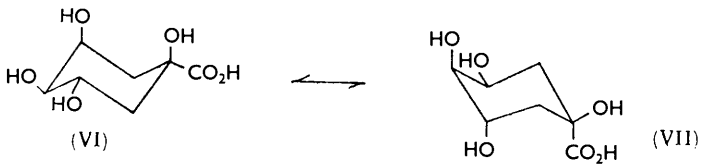
(V)

The synthesis of 3-*O*-galloylquinic acid (I; R^1 = R^2 = R^4 = R^5 = H, R^3 = 3,4,5-trihydroxybenzoyl) followed closely that of 3-*O*-*p*-coumaroylquinic acid described by Haslam, Haworth, and Makinson.[2] Tri-*O*-benzylgalloyl chloride with diphenylmethyl 1-*O*-ethoxycarbonyl-4,5-*O*-isopropylidenequinate [2] (V; R = H) gave the ester (V; R = tri-*O*-benzylgalloyl) from which the protecting groups were removed by successive treatment with alkali, hydrogenation, and acid hydrolysis, to give 3-*O*-galloylquinic acid, isolated as an amorphous solid after countercurrent distribution. Although chlorogenic acid (3-*O*-caffeoylquinic acid) gives both a crystalline penta-acetate and an isopropylidene derivative attempts to prepare analogous derivatives of 3-*O*-galloylquinic acid failed and the substance was characterised by analysis and optical rotation value.

The sole claim to specific acylation of quinic acid at the 4- or 5-position is that of Panizzi and his co-workers [13] in the synthesis of cynarin [1,4-di-*O*-caffeoylquinic acid (I; R^2 = R^3 = R^5 = H, R^1 = R^4 = 3,4-dihydroxycinnamoyl)]. They showed that condensation of equimolar proportions of 3,4-di-*O*-methoxycarbonylcinnamoyl chloride and 1-*O*-(3,4-di-*O*-methoxycarbonylcinnamoyl)quinide (IV; R^1 = 3,4-di-*O*-methoxycarbonylcinnamoyl, R^4 = R^5 = H), followed by controlled saponification, gave cynarin

[11] Josephson, *Ber.*, 1928, **61**, 911.
[12] Karrer and Link, *Helv. Chim. Acta*, 1927, **10**, 794.
[13] Panizzi, Scarpati, and Scarpati, *Gazzetta*, 1954, **84**, 806.

in small yield. In the synthesis of 4-*O*-galloylquinic acid (I; $R^1 = R^2 = R^3 = R^5 = H$, R^4 = 3,4,5-trihydroxybenzoyl) use has been made of the well authenticated [14,15] preferential acylation of an equatorial as opposed to an axial hydroxyl group attached to a cyclohexane ring. Heyns and Gottschalck,[16] and Haslam, Haworth, and Knowles [17] have shown that platinum-catalysed dehydrogenation of quinic acid gives 5-dehydroquinic acid, thus demonstrating (VI) as the preferred conformation of quinic acid. However, conversion of quinic acid into quinide (the 1,3-lactone) must initially involve change of quinic acid into the conformation (VII), and hence in quinide and its derivatives (IV) the 5-hydroxyl group is equatorial. Condensation of 1-*O*-ethoxycarbonylquinide with an equimolar proportion of ethyl chloroformate gave a crystalline diethoxycarbonyl ester which was therefore formulated as 1,5-di-*O*-ethoxycarbonylquinide (IV; $R^4 = H$, $R^1 = R^5 = CO_2Et$). The product showed three infrared carbonyl stretching frequencies, namely, 1795 (γ-lactone), 1760 (1-CO_2Et), and 1745 cm.$^{-1}$ (hydrogen-bonded 5-CO_2Et), and when condensed with tri-*O*-benzylgalloyl chloride gave the ester (IV; $R^1 = R^5 = CO_2Et$, R^4 = tri-*O*-benzylgalloyl). Hydrogenation of this ester, followed by hydrolysis in acetic acid, gave 4-*O*-galloylquinic acid which was separated from gallic acid and other artefacts by countercurrent distribution and isolated as an amorphous solid. Methylation of 4-*O*-galloylquinic acid with diazomethane gave an amorphous tetramethyl derivative which was not attacked by periodic acid, confirming the location of the galloyl group at position 4.



(VI) (VII)

Synthesis of 5-*O*-galloylquinic acid * (I; $R^1 = R^2 = R^3 = R^4 = H$, R^5 = 3,4,5-trihydroxybenzoyl) was achieved by condensing 1-*O*-ethoxycarbonylquinide (IV; $R^1 = CO_2Et$, $R^4 = R^5 = H$) with 1—2 mol. of tri-*O*-benzylgalloyl chloride. This gave an inseparable mixture of the 4- and the 5-*O*-(tri-*O*-benzylgalloyl) ester which, when hydrogenated and then treated with water at 100°, gave a complex mixture from which both 4- and 5-*O*-galloylquinic acid were isolated by countercurrent distribution; the predominance of the 5-*O*-galloyl derivative in the products is consistent with the preferential acylation of the equatorial 5-hydroxyl group in compound (IV; $R^1 = CO_2Et$, $R^4 = R^5 = H$). Small amounts of both 4- and 5-*O*-galloylquinic acid were also obtained on controlled hydrolysis of the amorphous 4,5-di-*O*-galloylquinic acid (I; $R^1 = R^2 = R^3 = H$, $R^4 = R^5$ = 3,4,5-trihydroxybenzoyl); the latter was prepared by condensation of tri-*O*-benzylgalloyl chloride with (IV; $R^1 = CO_2Et$, $R^4 = R^5 = H$), followed by hydrogenation and rupture of the lactone ring in water. The amorphous 5-*O*-galloylquinic acid gave with diazomethane a methylated derivative which consumed approximately 1 mol. of periodic acid, indicating the presence of an α-glycol grouping and hence position 5 for galloylation. Attempts to prepare lactone derivatives by heating 4- and 5-*O*-galloylquinic acid in acetic acid were unsuccessful and paper chromatography indicated that in both cases lactonisation was accompanied by some migration of the galloyl group to the 5- and 4-position, respectively.

* Designation of this compound as a 5- rather than a 3-*O*-galloyl derivative is based on the numbering shown in formula (I) and depends on the stereochemistry. If such compounds were named as derivatives of 1,3,4,5-tetrahydroxycyclohexanecarboxylic acid with the stereochemistry designated by, say, the *R*,*S* system, the present compound would be a 3-ester.—Ed.

[14] Barton and Morrison, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 184.
[15] Orloff, *Chem. Rev.*, 1954, **54**, 347.
[16] Heyns and Gottschalck, *Chem. Ber.*, 1961, **94**, 343.
[17] Haslam, Haworth, and Knowles, *J.*, 1962, 1854.

The mono-*O*-galloylquinic acids were all isolated as amorphous solids and only in the case of 1-*O*-galloylquinic acid was it possible to isolate a crystalline derivative. The characterisation of these substances has therefore been predominantly by optical rotation, countercurrent distribution, and paper-chromatographic pattern, but the last property alone is deemed an insufficient criterion in the absence of other results to confirm the structure of theogallin [6] as 3-*O*-galloylquinic acid.

The basic " core " of several gallotannins has been elucidated by Haworth and his co-workers,[7,8,18] using methanolysis. In this way [8] a tri-*O*-galloylquinic acid, formulated, as a result of methylation experiments, as 3,4,5-tri-*O*-galloylquinic acid was identified as the " core " of Tara gallotannin, and its structure has now been confirmed by unambiguous synthesis. Treatment of 4,5-*O*-isopropylidenequinide (III; R = H) with benzyl iodide and silver oxide gave small yields of 1-*O*-benzyl-4,5-isopropylidenequinide (III; R = CH_2Ph) which on acidic and alkaline hydrolysis afforded 1-*O*-benzylquinic acid as a gum. Condensing tri-*O*-benzylgalloyl chloride with diphenylmethyl 1-*O*-benzylquinate (prepared by the action of diphenyldiazomethane) gave the tristri-*O*-benzylgalloyl ester (I; R^1 = CH_2Ph, R^2 = $CHPh_2$, R^3 = R^4 = R^5 = tri-*O*-benzylgalloyl) which on hydrogenation yielded 3,4,5-tri-*O*-galloylquinic acid as an amorphous solid, separating from water as a gel. The product was identical with the previous methanolysis product of Tara gallotannin.

A further galloylated quinic acid derivative prepared during this work was tetra-*O*-galloylquinic acid. Quinic acid and diphenyldiazomethane gave the diphenylmethyl ester which with tri-*O*-benzylgalloyl chloride gave the tetrakistri-*O*-benzylgalloyl ester (I; R^2 = $CHPh_2$, R^1 = R^3 = R^4 = R^5 = tri-*O*-benzylgalloyl). Hydrogenation then yielded the amorphous tetra-*O*-galloylquinic acid which also separated from water as a gel.

Experimental

Alumina refers to Spence's grade H, washed with ethyl acetate and reactivated at 140°. Paper-chromatographic methods and procedures used for the preparation of samples for quantitative analysis are as described in Part III.[7]

4,5-O-*Isopropylidene*-1-O-(*tri*-O-*benzylgalloyl*)*quinide*.—A solution of tri-*O*-benzylgalloyl chloride [9] (6·5 g.) and 4,5-*O*-isopropylidenequinide [10] (2·5 g.) was heated in chloroform (40 c.c.) containing pyridine (10 c.c.) at 40° for 10 days, and then diluted with chloroform (100 c.c.), washed successively with ice-cold 2N-sulphuric acid (2 × 100 c.c.), 3% sodium carbonate solution (3 × 10 c.c.), and water (100 c.c.), and dried ($MgSO_4$). Removal of the solvent gave 4,5-O-*isopropylidene*-1-O-(*tri*-O-*benzylgalloyl*)*quinide* (3·5 g.) which crystallised in needles [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 163—164° (Found: C, 71·4; H, 5·7. $C_{38}H_{36}O_9$ requires C, 71·7; H, 5·8%), $[\alpha]_D^{25}$ +5·1° (*c* 1·8 in $CHCl_3$), $\nu_{max.}$ (KBr disc) 1792 and 1717 cm.$^{-1}$.

1-O-*Galloyl*-4,5-O-*isopropylidenequinide*.—A solution of 4,5-*O*-isopropylidene-1-*O*-(tri-*O*-benzylgalloyl)quinide (1·85 g.) in ethyl acetate was reduced in hydrogen in the presence of palladium–charcoal (0·20 g.) until uptake ceased (195 c.c.). Removal of the catalyst and solvent and crystallisation of the residue from acetone–water gave 1-*O*-galloyl-4,5-*O*-isopropylidenequinide (0·91 g.) as plates, m. p. 275—276° (Found: C, 56·0; H, 5·2. $C_{17}H_{18}O_9$ requires C, 55·7; H, 5·0%), $\nu_{max.}$ (KBr disc) 1780 and 1715 cm.$^{-1}$.

Ethyl 1-O-*Galloylquinate*.—A solution of 4,5-*O*-isopropylidene-1-*O*-(tri-*O*-benzylgalloyl-quinide (2·02 g.) in ethanol (75 c.c.) was heated to 60° and stirred by a stream of nitrogen whilst 0·408N-barium hydroxide (7·78 c.c.) was added during ¾ hr. After cooling, the solution was acidified with N-sulphuric acid and extracted with ethyl acetate (3 × 50 c.c.). Evaporation gave a gum which was treated with 80% acetic acid (100 c.c.) at 100° for 2 hr., whereafter removal of the solvent gave a gum which was shaken in ethyl acetate (50 c.c.) in hydrogen with 10% palladium–charcoal (0·2 g.), until uptake (200 c.c.) ceased. The catalyst was removed and paper chromatography in (A) 6% acetic acid and (B) butan-2-ol–acetic acid–water (14 : 1 : 5) of the solution disclosed gallic acid R_F 0·45, 0·66, ethyl gallate, R_F 0·55, 0·88, and 1-*O*-galloylquinate, R_F 0·76, 0·58, and an unknown substance, R_F 0·80, 0·90, respectively. Evaporation

[18] Armitage, Haslam, Haworth, and Searle, *J.*, 1962, 3808.

of the ethyl acetate gave a gum which was subjected to countercurrent distribution between ethyl acetate and water (40 tubes, phase-volume 95 c.c.). The contents of each tube were analysed by paper chromatography and concentration of tubes 4—13 gave a gum from which *ethyl* 1-O-*galloylquinate* (0·4 g.) crystallised in plates (from water), m. p. 232—234° (Found: C, 51·5; H, 5·7. $C_{16}H_{20}O_{10}$ requires C, 51·5; H, 5·4%), $[\alpha]_D^{21}$ −6·6° (*c* 0·45 in H_2O), $\nu_{max.}$ (KBr disc) 1727 and 1623 cm.$^{-1}$.

1-O-(*Tri*-O-*benzylgalloyl*)*quinide*.—4,5-*O*-Isopropylidene-1-*O*-(tri-*O*-benzylgalloyl)quinide (2·25 g.) was heated in 80% acetic acid (100 c.c.) at 100° for 2 hr., then removal of the solvent gave a gum which was dissolved in ethyl acetate (100 c.c.), washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave 1-O-(*tri*-O-*benzylgalloyl*)-*quinide* (0·52 g.) as needles, m. p. 122° (Found: C, 70·2; H, 5·6. $C_{35}H_{32}O_9$ requires C, 70·5; H, 5·4%), $[\alpha]_D^{25}$ −12·2° (*c* 1·5 in $CHCl_3$), $\nu_{max.}$ (KBr disc) 1775 and 1715 cm.$^{-1}$.

1-O-*Galloylquinide*.—A solution of 1-*O*-(tri-*O*-benzylgalloyl)quinide (1·47 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen with 10% palladium–charcoal (0·15 g.) until uptake ceased (165 c.c.), then the catalyst and solvent were removed. Crystallisation of the residue from water gave 1-O-*galloylquinide* (0·5 g.) as needles, m. p. 258—260° (Found: C, 51·4; H, 4·5. $C_{14}H_{14}O_9$ requires C, 51·5; H, 4·3%), $[\alpha]_D^{23}$ −19·2° (*c* 1·0 in acetone), $\nu_{max.}$ (KBr disc) 1770 and 1690 cm.$^{-1}$.

1-O-*Galloylquinic Acid*.—A solution of 1-*O*-galloylquinide (0·65 g.) in water (130 c.c.) was kept at 100° for 40 hr., whereafter paper chromatography revealed 1-*O*-galloylquinide, R_F (A) 0·54, (B) 0·62, gallic acid, R_F (A) 0·45, (B) 0·66, and 1-*O*-galloylquinic acid, R_F (A) 0·69, (B) 0·34. Removal of the solvent at 30° gave a gum which was subjected to countercurrent distribution between ethyl acetate and water (phase volume 40 c.c.; 50 transfers), and the contents of the tubes were analysed by paper chromatography. Concentration of the contents of tubes 2—6 gave, after freeze-drying from water, 1-O-*galloylquinic acid* as an amorphous powder (0·29 g.) (Found: C, 48·9; H, 4·8. $C_{14}H_{16}O_{10}$ requires C, 48·8; H, 4·7%), $[\alpha]_D^{25}$ −13·6° (*c* 0·77 in H_2O), $\nu_{max.}$ (KBr disc) at 1690 cm.$^{-1}$.

Action of Sodium Hydrogen Carbonate Solution on 1-O-*Galloylquinic Acid*.—1-*O*-Galloylquinic acid (0·01 g.) was heated in saturated sodium hydrogen carbonate solution (1 c.c.) at 60° and samples were withdrawn after 5, 10, 15, 30, and 60 min., acidified with acetic acid, and subjected to paper chromatography. After 15 min. unchanged 1-*O*-galloylquinic acid, R_F (A) 0·69, (B) 0·34, 3-*O*-galloylquinic acid, R_F (A) 0·62 (B) 0·46, and gallic acid, R_F (A) 0·45, (B) 0·66, were detected.

Repetition of the reaction in the presence of ethanol (1 c.c.) showed after 15 min. the additional presence of ethyl gallate, R_F (A) 0·55, (B) 0·88.

Conversion of 1-O-*Galloylquinic Acid into* 1-O-*Galloylquinide*.—A solution of 1-*O*-galloylquinic acid (0·15 g.) in glacial acetic acid (50 c.c.) was heated at 100° for 6 hr., then removal of the solvent gave a gum which was subjected to countercurrent distribution between ethyl acetate and water (50 transfers; phase volume 15 c.c.). The contents of the tubes were analysed by paper chromatography; evaporation of material in tubes 26—36 and crystallisation of the residues from water gave 1-*O*-galloylquinide (0·075 g.) as needles, m. p. and mixed m. p. 258—260°.

Diphenylmethyl 1-O-*Ethoxycarbonyl*-4,5-O-*isopropylidene*-3-O-(*tri*-O-*benzylgalloyl*)*quinate*.—Diphenylmethyl 1-*O*-ethoxycarbonyl-4,5-*O*-isopropylidenequinate [2] (5·0 g.) and tri-*O*-benzylgalloyl chloride (11·5 g.) were kept in chloroform (80 c.c.) containing pyridine (20 c.c.) at 60° for 10 days, then the solution was diluted with chloroform (100 c.c.), shaken with ice-cold N-sulphuric acid (3 × 100 c.c.), 3% sodium carbonate solution (3 × 100 c.c.), and water (100 c.c.), and dried ($MgSO_4$). Removal of the solvent gave a gum which was dissolved in benzene (50 c.c.) and kept for 12 hr. Then the precipitated tri-*O*-benzylgallic anhydride,[19] m. p. and mixed m. p. 166—167°, was collected. The filtrate was diluted with chloroform (50 c.c.) and passed down a column of alumina (250 g.), and elution was continued with 1 : 1 benzene–chloroform. Removal of the solvent from the eluate (250 c.c.) gave *diphenylmethyl* 1-O-*ethoxycarbonyl*-4,5-O-*isopropylidene*-3-O-(*tri*-O-*benzylgalloyl*)*quinate*, which after crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) formed needles (6·8 g.), m. p. 178—180° (Found: C, 72·9; H, 6·1. $C_{54}H_{52}O_{12}$ requires C, 72·7; H, 5·9%), $\nu_{max.}$ (KBr disc) 1750 and 1705 cm.$^{-1}$.

3-O-*Galloylquinic Acid*.—To a solution of the above ester (3·33 g.) in tetrahydrofuran (50

[19] Schmidt and Schach, *Annalen*, 1959, **571**, 29.

c.c.) and water (10 c.c.), 0·43N-barium hydroxide (8·6 c.c.) was added during 1 hr., with stirring by nitrogen. The solution was neutralised with N-sulphuric acid and extracted with ethyl acetate (4 × 50 c.c.) and the extract dried ($MgSO_4$). Evaporation of the solvent gave a gum which was shaken in ethyl acetate (100 c.c.) and with 10% palladium–charcoal (0·3 g.) and hydrogen (uptake 410 c.c.). Removal of the catalyst and solvent gave a gum which was treated with 30% acetic acid (50 c.c.) at 100° for 2 hr. Paper chromatography of the residue obtained on removal of the acetic acid showed the presence of 3-*O*-galloylquinic acid, R_F (A) 0·62, (B) 0·46, gallic acid, R_F (A) 0·45, (B) 0·66, and an unidentified compound, R_F (A) 0·66, (B) 0·68, which were separated by countercurrent distribution between water and ethyl acetate (50 transfers; phase volume 40 c.c.). Analysis of the tube contents by paper chromatography and concentration of the contents of tubes 2—9 gave 3-O-*galloylquinic acid* as a white amorphous solid after freeze-drying from water (Found: C, 48·6; H, 5·0. $C_{14}H_{16}O_{10}$ requires C, 48·8; H, 4·7%), $[\alpha]_D^{22}$ −41·3° (*c* 0·73 in H_2O), $\nu_{max.}$ (KBr disc) 1690 cm.$^{-1}$.

1-O-*Ethoxycarbonylquinide*.—1-*O*-Ethoxycarbonyl-4,5-*O*-isopropylidenequinide (4·0 g.) was heated in 40% acetic acid (100 c.c.) at 100° for 1 hr., the solvent removed at 30°, and the residual gum dissolved in ethyl acetate (50 c.c.), washed with saturated sodium hydrogen carbonate solution (2 × 50 c.c.) and water (50 c.c.), and dried ($MgSO_4$). Removal of the solvent and crystallisation of the gummy residue from benzene gave 1-O-*ethoxycarbonylquinide* as needles (2·5 g.), m. p. 100—101° (Found: C, 49·0; H, 5·9. $C_{10}H_{14}O_7$ requires C, 48·8; H, 5·7%), $[\alpha]_D^{22}$ −1·7° (*c* 1·5 in $CHCl_3$), $\nu_{max.}$ (KBr disc) 1780 and 1750 cm.$^{-1}$.

1,5-*Di*-O-*ethoxycarbonylquinide*.—To 1-*O*-ethoxycarbonylquinide (2·7 g.) in chloroform (40 c.c.) and pyridine (2·5 c.c.), cooled to 0°, was added in ¼ hr. ethyl chloroformate (1·2 c.c.), and the mixture was kept at room temperature for 12 hr. before dilution with chloroform (50 c.c.) and washing with ice-cold N-sulphuric acid (50 c.c.), 4% sodium carbonate solution (25 c.c.), and water (50 c.c.). After drying ($MgSO_4$), the solvent was removed, to give a glass which was dissolved in benzene (50 c.c.) and filtered through alumina (60 g.). Evaporation of the benzene from the eluate and crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the *diethoxycarbonyl ester* as needles (0·50 g.), m. p. 113—114° (Found: C, 48·8; H, 5·4. $C_{13}H_{18}O_9$ requires C, 49·1; H, 5·7%), $[\alpha]_D^{22}$ −10·4° (*c* 1·4 in $CHCl_3$), $\nu_{max.}$ (in Nujol) at 1795, 1760, and 1745 cm.$^{-1}$.

1,5-*Di*-O-*ethoxycarbonyl*-4-O-(*tri*-O-*benzylgalloyl*)*quinide*.—A solution of the preceding ester (0·47 g.) and tri-*O*-benzylgalloyl chloride (1·40 g.) in chloroform (10 c.c.) containing pyridine (2·5 c.c.) was kept at 60° for 12 days, then the solution was diluted with chloroform (20 c.c.), washed with ice-cold N-sulphuric acid (20 c.c.), 4% sodium carbonate solution (20 c.c.), and water (2 × 20 c.c.), and dried ($MgSO_4$). Evaporation of the chloroform gave a gum which was dissolved in benzene (15 c.c.) and kept for 24 hr. After collection of the crystalline tri-*O*-benzylgallic anhydride,[19] m. p. and mixed m. p. 166—167°, the filtrate was adsorbed on alumina (30 g.) and eluted with 1 : 1 benzene–chloroform (100 c.c.). Removal of the solvents and crystallisation from benzene–light petroleum (b. p. 60—80°) gave needles (0·40 g.) of 1,5-*di*-O-*ethoxycarbonyl*-4-O-(*tri*-O-*benzylgalloyl*)*quinide*, m. p. 125—126° (Found: C, 66·3; H, 5·4. $C_{41}H_{40}O_{13}$ requires C, 66·5; H, 5·4%), $\nu_{max.}$ (in Nujol) at 1800, 1760, and 1730 cm.$^{-1}$.

4-O-*Galloylquinic Acid*.—1,5-Di-*O*-ethoxycarbonyl-4-*O*-(tri-*O*-benzylgalloyl)quinide (0·75 g.) in ethyl acetate (30 c.c.) was shaken with 10% palladium–charcoal (0·1 g.) in hydrogen (uptake 70 c.c.). Removal of the catalyst and solvent and treatment of the residue with 50% acetic acid (45 c.c.) at 100° for 24 hr. gave a mixture which paper chromatography showed to contain 4-*O*-galloylquinic acid, R_F (A) 0·68, (B) 0·42, gallic acid, R_F (A) 0·45, (B) 0·66, and small amounts of unidentified substances, R_F (A) 0·76, (B) 0·25, and (A) 0·80, (B) 0·65. The acetic acid was removed at 30° and the residue subjected to countercurrent distribution between ethyl methyl ketone and water (120 transfers, phase volume 15 c.c.). Analysis by paper chromatography and concentration of material in tubes 38—52 gave, after freeze-drying from water, 4-O-*galloylquinic acid* (0·20 g.) as a white amorphous powder (Found: C, 48·7; H, 4·9. $C_{14}H_{16}O_{10}$ requires C, 48·8; H, 4·7%), $[\alpha]_D^{23}$ −37° (*c* 0·95 in acetone), $\nu_{max.}$ (KBr disc) 1700 cm.$^{-1}$.

4- *and* 5-O-*Galloylquinic Acid*.—A solution of 1-*O*-ethoxycarbonylquinide (4·0 g.) and tri-*O*-benzylgalloyl chloride (9·0 g.) in chloroform (55 c.c.) containing pyridine (15 c.c.) was kept at 60° for 11 days, then the solution was diluted with chloroform (50 c.c.), washed with N-sulphuric acid (2 × 50 c.c.), 3% aqueous sodium carbonate (2 × 50 c.c.), and water (50 c.c.), and dried ($MgSO_4$). Evaporation gave a gum which was dissolved in benzene (25 c.c.) and kept for 24 hr. Crystalline tri-*O*-benzylgallic anhydride,[19] m. p. and mixed m. p. 166—167°, was

separated and the filtrate adsorbed on alumina (200 g.) which was then eluted with benzene–chloroform (2 : 1; 300 c.c.). Evaporation of the eluate and freeze-drying of the residue from benzene gave a white amorphous solid (6·2 g.) (Found: C, 67·9; H, 5·4%), $\nu_{max.}$ (in Nujol) 1800 and 1740 cm.$^{-1}$. This product was shaken in ethyl acetate (75 c.c.) with 10% palladium–charcoal (0·6 g.) and hydrogen for 15 hr. (uptake 620 c.c.). After separation of the catalyst and evaporation of the ethyl acetate and toluene the resultant gum was heated at 100° in water (150 c.c.) for 24 hr., whereafter chromatography showed the presence of 4-*O*-galloylquinic, R_F (A) 0·68, (B) 0·42, 5-*O*-galloylquinic, R_F (A) 0·72, (B) 0·28, and gallic acid, R_F (A) 0·45, (B) 0·66, and substances tentatively identified as 4-*O*-galloylquinide, R_F (A) 0·65, (B) 0·60, and 5-*O*-galloylquinide, R_F (A) 0·60, (B) 0·58. Removal of the water gave a gum which was subjected to countercurrent distribution between ethyl methyl ketone and water (120 transfers, phase volume 40 c.c.), and the tube contents were analysed by paper chromatography. Concentration of material in tubes 12—24 gave 5-O-*galloylquinic acid* (0·35 g.) as a white amorphous powder (after freeze-drying from water) (Found: C, 48·7; H, 5·0. $C_{14}H_{16}O_{10}$ requires C, 48·8; H, 4·7%), $[\alpha]_D^{21}$ −15·4° (*c* 1·5 in H_2O), $\nu_{max.}$ (KBr disc) 1700 cm.$^{-1}$. Concentration of material in tubes 25—41 and freeze-drying from water gave an amorphous powder (1·25 g.) which paper chromatography showed to be a mixture of 4- and 5-*O*-galloylquinic acid. Material in tubes 42—48, on concentration and freeze-drying from water, gave a white amorphous powder (0·20 g.), consisting of 4-*O*-galloylquinic acid (Found: C, 48·6; H, 5·0%).

Periodate Oxidation of 4- *and* 5-O-*Galloylquinic Acid.*—To a solution of the galloylquinic acid (0·30 g.) in acetone (10 c.c.) was added ethereal diazomethane (50 c.c.) (prepared from 3·5 g. of *N*-nitrosomethylurea), and the mixture was kept at 5° overnight, whereafter the solvents were removed and the process was repeated. The resultant gum was dissolved in benzene and filtered through alumina (6 g.), the benzene removed, and the product (0·3 g.) freeze-dried from benzene. To each product was added a solution of sodium metaperiodate (0·175 g. in 25 c.c.) and the mixtures were left for 3 hr. at room temperature. The excess of metaperiodate was determined by addition of potassium iodide and titration of the liberated iodine against 0·1N-sodium thiosulphate. The results are discussed on p. 2175.

1-O-*Ethoxycarbonyl*-4,5-*di*-O-(*tri*-O-*benzylgalloyl*)*quinide.*—Tri-*O*-benzylgalloyl chloride (14·0 g.) and 1-*O*-ethoxycarbonylquinide (1·9 g.) were dissolved in chloroform (55 c.c.) containing pyridine (15 c.c.) and kept at 60° for 14 days, then diluted with chloroform (50 c.c.), washed with ice-cold N-sulphuric acid (2 × 100 c.c.), 4% sodium carbonate solution (2 × 100 c.c.), and water (2 × 50 c.c.), and dried ($MgSO_4$). Removal of the chloroform gave a gum which was dissolved in benzene (50 c.c.) and kept at room temperature for 24 hr. The precipitated tri-*O*-benzylgallic anhydride [19] was collected. The filtrate was adsorbed on alumina (350 g.) and elution carried out with the same solvent (200 c.c.). Removal of the benzene and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 1-O-*ethoxycarbonyl*-4,5-*di*-O-(*tri*-O-*benzylgalloyl*)*quinide* as needles (3·1 g.), m. p. 152—153° (Found: C, 72·7; H, 5·4. $C_{66}H_{58}O_{15}$ requires C, 72·7; H, 5·4%), $[\alpha]_D^{18}$ +69° (*c* 1·7 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 1800, 1750, and 1740 cm.$^{-1}$.

1-O-*Ethoxycarbonyl*-4,5-*di*-O-*galloylquinide.*—The above ester (1·8 g.) in ethyl acetate (15 c.c.) was hydrogenated in the presence of 10% palladium–charcoal (0·2 g.) until uptake (230 c.c.) ceased. Separation of the catalyst, removal of the solvent, and crystallisation of the residue from acetone–water gave needles (0·45 g.) of 1-O-*ethoxycarbonyl*-4,5-*di*-O-*galloylquinide*, m. p. 128—130° (Found: C, 52·5; H, 4·1. $C_{24}H_{22}O_{15}$ requires C, 52·4; H, 4·0%), $\nu_{max.}$ (in Nujol) 1790, 1750, and 1705 cm.$^{-1}$.

4,5-*Di*-O-*galloylquinic Acid.*—A solution of 1-*O*-ethoxycarbonyl-4,5-di-*O*-galloylquinide (2·2 g.) in water (200 c.c.) was refluxed for 7 hr., then concentrated to 40 c.c. and subjected to countercurrent distribution between ethyl acetate and water (50 transfers, phase volume 40 c.c.). The contents of the tubes were analysed by paper chromatography and concentration of material in tubes 2—15 gave a product which analysis showed to consist predominantly of 4,5-di-*O*-galloylquinic acid, R_F (A) 0·51, (B) 0·44. This was dissolved in N-acetic acid (20 c.c.) and applied to cellulose (4 × 60 cm.). Elution was with N-acetic acid. Fractions (15 c.c.) were collected and analysed by measurement of their optical density at 320 mμ. Concentration of fractions 40—63, dissolution of the residue in water (20 c.c.), extraction with ethyl acetate (5 × 50 c.c.), removal of the solvent, and freeze-drying from water gave 4,5-*di*-O-*galloylquinic acid* as a white amorphous solid (0·6 g.) (Found: C, 50·8; H, 4·4. $C_{21}H_{20}O_{14}$ requires C, 50·8; H, 4·1%), $[\alpha]_D^{19}$ −58·2° (*c* 0·93 in acetone), $\nu_{max.}$ (KBr disc) 1710 cm.$^{-1}$.

Hydrolysis of 4,5-*Di*-O-*galloylquinic Acid*.—The above acid (2·0 g.) was heated with 0·5N-hydrochloric acid (200 c.c.) at 100° for 6 hr. and, after cooling, extracted with ethyl methyl ketone (4 × 50 c.c.). After evaporation the residue was subjected to countercurrent distribution between ethyl methyl ketone and water (120 transfers, phase volume 40 c.c.). The contents of the tubes were analysed by paper chromatography, material in appropriate tubes was concentrated, and the products were freeze-dried from water. Tubes 12—22 gave 5-*O*-galloylquinic acid (0·15 g.), R_F (A) 0·72, (B) 0·28. Tubes 41—48 gave 4-*O*-galloylquinic acid (0·11 g.), R_F (A) 0·68, (B) 0·42.

1-O-*Benzyl*-4,5-O-*isopropylidenequinide*.—A mixture of benzyl iodide (20 g.), silver oxide (60 g.), and 4,5-*O*-isopropylidenequinide (10 g.) in chloroform (50 c.c.) was stirred under reflux for 24 hr. After removal of the silver salts the solution was filtered through alumina (100 g.) and elution carried out with benzene–chloroform (2 : 1). Evaporation of the eluate (250 c.c.) gave a gum which, after treatment with charcoal in ethyl acetate, was extracted with light petroleum (b. p. 60—80°) (4 × 100 c.c.). The residue obtained from this extract crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give 1-O-*benzyl*-4,5-O-*isopropylidenequinide* (1·1 g.) as needles, m. p. 137—139° (Found: C, 67·4; H, 6·5. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%), $\nu_{max.}$ (in Nujol) 1780 cm.$^{-1}$.

1-O-*Benzylquinide*.—1-*O*-Benzyl-4,5-*O*-isopropylidenequinide (1·05 g.) was heated at 100° for 2 hr. with 80% acetic acid (50 c.c.). Evaporation and crystallisation of the residue from benzene gave 1-O-*benzylquinide* (0·80 g.) as needles, m. p. 129—130° (Found: C, 63·5; H, 6·0. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%), $\nu_{max.}$ (KBr disc) 1780 cm.$^{-1}$.

Diphenylmethyl 1-O-*Benzylquinate*.—1-*O*-Benzylquinide (0·65 g.) was treated with N-sodium hydroxide (3·0 c.c.) for 30 min. at room temperature, acidified with N-hydrochloric acid, and extracted with ethyl acetate (5 × 25 c.c.). Evaporation of the solvent gave a gum which was dried (P_2O_5; 0·05 mm.) and treated with diphenyldiazomethane (0·65 g.) in dioxan (20 c.c.), first at room temperature for 1 hr. and then at 60° for 6 hr. Removal of the dioxan and freeze-drying of the residue from benzene gave as an amorphous solid *diphenylmethyl* 1-O-*benzylquinate* (0·6 g.) (Found: C, 72·4; H, 6·0. $C_{27}H_{28}O_6$ requires C, 72·3; H, 6·3%), $[\alpha]_D^{24}$ +1·1° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ (KBr disc) 1730 cm.$^{-1}$. It separated as a gel from ethyl acetate–light petroleum (b. p. 60—80°).

Diphenylmethyl 1-O-*Benzyl*-3,4,5-*tris*-O-(*tri*-O-*benzylgalloyl*)*quinate*.—Diphenylmethyl 1-*O*-benzylquinate (0·5 g.) and tri-*O*-benzylgalloyl chloride (3·0 g.) were heated in chloroform (20 c.c.) and pyridine (5 c.c.) at 60° for 20 days, then diluted with chloroform (50 c.c.), washed with ice-cold N-sulphuric acid (2 × 50 c.c.), 3% aqueous sodium carbonate (50 c.c.), and water (50 c.c.), and dried ($MgSO_4$). Removal of the chloroform gave a gum which was dissolved in benzene (20 c.c.) and the tri-*O*-benzylgallic anhydride [19] which separated was collected. The filtrate was concentrated to 10 c.c., a further small amount of the anhydride collected, and the remaining filtrate added to alumina (70 g.) which was eluted with benzene (100 c.c.). Evaporation of the benzene from the eluate and freeze-drying of the residue from benzene gave *diphenyl* 1-O-*benzyl*-3,4,5-*tris*-O-(*tri*-O-*benzylgalloyl*)*quinate* as an amorphous solid (0·6 g.) (Found: C, 77·4; H, 5·5. $C_{111}H_{94}O_{18}$ requires C, 77·4; H, 5·5%), $[\alpha]_D^{25}$ −61·7 (*c* 0·86 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 1720 cm.$^{-1}$.

3,4,5-*Tri*-O-*galloylquinic Acid*.—The above ester (0·55 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen with 10% palladium–charcoal (0·3 g.) until uptake ceased (75 c.c.). Separation of the catalyst and removal of the solvent gave a gum which was subjected to countercurrent distribution in solvent system e [7] (50 transfers, phase volume 15 c.c.). Concentration of the contents of tubes 12—26 after paper chromatography gave 3,4,5-tri-*O*-galloylquinic acid (0·11 g.) which was obtained as a white amorphous powder after freeze-drying from water (Found: C, 52·0; H, 4·0. Calc. for $C_{28}H_{24}O_{18}$: C, 51·8; H, 3·7%), $[\alpha]_D^{23}$ −130° (*c* 1·8 in water), $\nu_{max.}$ (KBr disc) 1700 cm.$^{-1}$, R_F (A) 0·34, (B) 0·50 {Haslam, Haworth, and Keen [8] give $[\alpha]_D$ −129·0°, $\nu_{max.}$ (KBr disc) 1700 cm.$^{-1}$, R_F (A) 0·32, (B) 0·52.

Diphenylmethyl Quinate.—A dioxan solution (250 c.c.) of quinic acid (10 g.) and diphenyldiazomethane (16 g.) was refluxed until the solution was pale straw-coloured (6 hr.), then evaporated to give a gum which was dissolved in ethyl acetate (100 c.c.), washed with aqueous sodium hydrogen carbonate (2 × 50 c.c.), and water (50 c.c.), and dried ($MgSO_4$). Removal of the ethyl acetate and crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave *diphenylmethyl quinate* (1·5 g.) as plates, m. p. 125—126° (Found: C, 66·7; H, 6·2. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), $\nu_{max.}$ (KBr disc) 1740 cm.$^{-1}$.

Diphenylmethyl Tetrakis-O-(tri-O-benzylgalloyl)quinate.—A mixture of tri-*O*-benzylgalloyl chloride (16·0 g.) and diphenylmethyl quinate (1·0 g.) in chloroform (55 c.c.) containing pyridine (15 c.c.) was heated at 60° for 25 days, then diluted with chloroform (50 c.c.), washed with N-sulphuric acid (2 × 100 c.c.) and water (2 × 100 c.c.), and dried ($MgSO_4$). The gum obtained on evaporation of the ethyl acetate was dissolved in benzene (20 c.c.) and kept for 24 hr. and the crystalline tri-*O*-benzylgallic anhydride,[19] m. p. and mixed m. p. 166°, was collected. The filtrate was chromatographed on alumina (200 g.) with benzene (350 c.c.) as eluant. Removal of the solvent from the eluate and freeze-drying from benzene gave the *ester* as a white amorphous solid (3·2 g.) (Found: C, 77·3; H, 5·3. $C_{132}H_{110}O_{22}$ requires C, 77·4; H, 5·4%), $[\alpha]_D^{22}$ −56° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ (in Nujol) 1710 $cm.^{-1}$.

Tetra-O-galloylquinic Acid.—Diphenylmethyl tetrakis-*O*-(tri-*O*-benzylgalloyl)quinate (3·0 g.) was reduced in ethyl acetate (50 c.c.) over 10% palladium–charcoal (0·30 g.), fresh catalyst (0·3 g.) being added after 12 and again after 24 hr. Separation of the catalyst and solvent gave a gum which was subjected to countercurrent distribution (50 transfers, phase volume (40 c.c.) between ethyl acetate and water. Concentration of material in tubes 15—30 gave a gum which was dissolved in water (20 c.c.). The solution was concentrated to 5 c.c. at 30°. *Tetra-O-galloylquinic acid* (0·4 g.) separated as a gel which, on drying (P_2O_5; 0·05 mm.), was an amorphous powder which shrank at 205—206° and melted 237—240° (Found: C, 52·6; H, 3·8. $C_{35}H_{28}O_{22}$ requires C, 52·5; H, 3·5%), $[\alpha]_D^{24}$ −177° (*c* 0·77 in H_2O), $\nu_{max.}$ (KBr disc) 1700 $cm.^{-1}$, R_F (A) 0·22, (B) 0·42.

The authors thank the Department of Scientific and Industrial Research for a maintenance grant (to D. A. L.) and Imperial Chemical Industries Limited for a grant for chemicals

Department of Chemistry, The University,
Sheffield, 10. [*Received, November 8th,* 1962.]