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THE SYNTHESIS OF 2- AND 3-GALLOYL DERIVATIVES OF ARBUTIN

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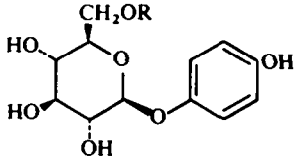
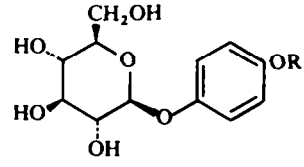
Abstract—The synthesis of 2 and 3 and 2,3 bisgalloyl and 4-O-methylgalloyl derivatives of arbutin is described. Attempts to convert the 2 aroyl derivatives to the C-glucoside bergenin in a biogenetically patterned synthesis are summarized.

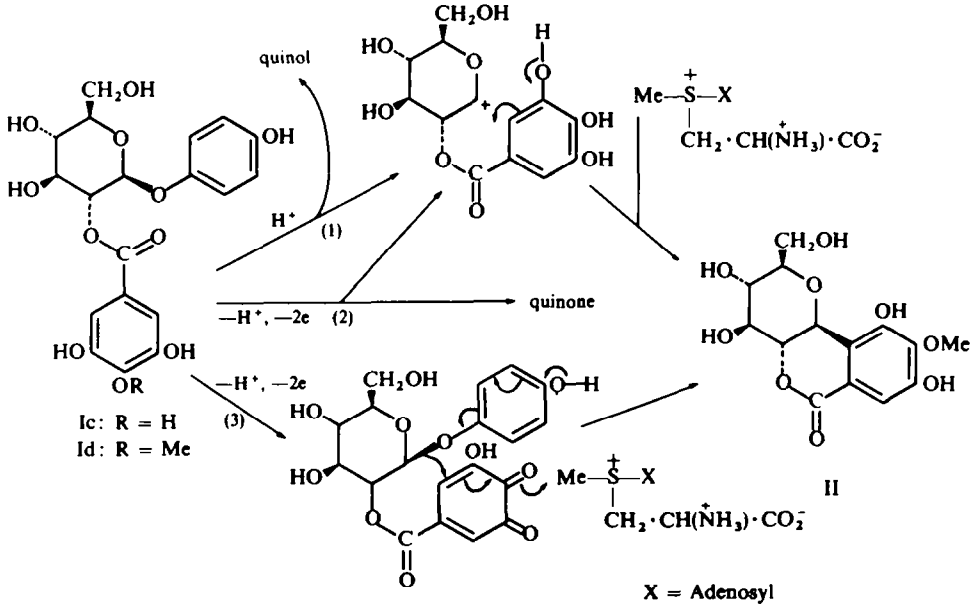
IN AN earlier paper[1] the isolation and identification of three monogalloyl esters of the phenolic glucoside arbutin (Ia, Ib and Ic) from the leaves of *Arctostaphylos uva ursi* was described. An identical distribution of these phenolic esters (Ia, Ib and Ic) may also be discerned in the leaf tissue of *Bergenia cordifolia* and *B. crassifolia.* In the



Ia: R = CO·C$_6$H$_2$(OH)$_3$—3,4,5

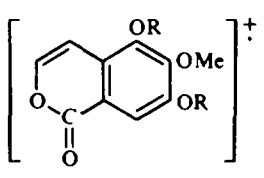


Ib: R = CO·C$_6$H$_2$(OH)$_3$—3,4,5

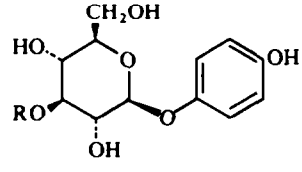


roots of *Bergenia* species however only the esters (Ia and Ib) are present and 2-O-galloylarbutin (Ic) is apparently replaced by the C-glucoside bergenin (II). This pattern of phenol distribution suggests a possible biogenetic relationship between the ester (Ic) and bergenin (II). For example it may be postulated that the phenolic esters are translocated from leaf to roots where further specific transformation of Ic occurs. Thus oxidative or acid catalysed displacement of the quinol residue followed by nucleophilic attack of the galloyl nucleus on the anomeric centre and finally methylation would lead to bergenin (routes 1 and 2). Similar mechanistic proposals were made earlier by Wenkert[2] who suggested 2-O-galloylglucose or its 1-phosphate, as a precursor of bergenin. An alternative route (3), which may be used to explain the unique position of methylation of the galloyl residue in bergenin, involves an internal redox reaction. Experiments designed to test these possibilities are described here.

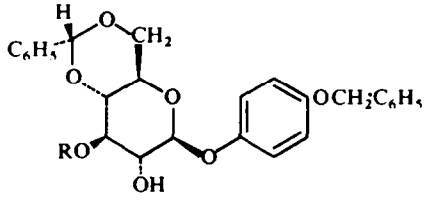
The synthesis of bergenin[3] establishes its β-glucosidic configuration and this was further confirmed by measurements of the PMR spectra of bergenin, its penta-acetate, di-O-methyl ether and tri-acetate, and penta-O-methyl bergenin. All showed the anomeric proton as a doublet centred around 5·15 to 5·25, J = 10 c/s indicating an approximately trans diaxial relationship with the proton at C-2. Thus if the β-glucoside 2-O-galloylarbutin (Ic) is a precursor of bergenin pathways (1) and (2) are only possible if the second stage is not concerted with the removal of the quinol residue and occurs preferentially from the β-side. The mass spectra of bergenin and its derivatives provide no definitive evidence regarding the β configuration but the presence of the ions (III, R = Me or R = —CO·Me) and associated fragment ions support the structural formulation II of Hay and Haynes[3] for bergenin.



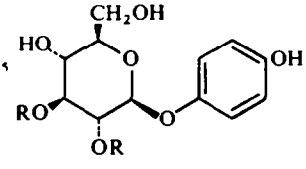
III



Ie: R = CO·$C_6H_2(OH)_3$—3,4,5
If: R = CO·$C_6H_2(OH)_2$—3,5—(OMe)—4



IVa: R = $CH_2 \cdot C_6H_5$
IVb: R = H



Va: R = CO·$C_6H_2(OH)_3$—3,4,5
Vb: R = CO·$C_6H_2(OH)_2$—3,5—(OMe)—4

Unambiguous synthesis of 2-O-galloylarbutin and its derivatives was not achieved since the preparation of the required glucose derivative IVa in an acceptable yield was not possible. Koenigs–Knorr condensation[4] of α-bromo-3-benzyl-2,4,6-tri-acetylglucose[5] with mono-O-benzylquinol under a variety of conditions gave IVa

in very poor yield (<2%). Condensation of tri-acetylgalloyl chloride and O-acetylquinol-3,4,6-tri-O-acetyl-β-D-glucoside[6] gave hepta-acetyl 2-O-galloylarbutin but predictably on treatment with base[1] a mixture of 2-, 3- and 6-O-galloylarbutin was identified by paper chromatography. The preparation of 2- and 3- galloyl- and 2,3-bisgalloylarbutin was carried out by condensation of tri-O-benzylgalloyl chloride with IVb, hydrogenation and counter-current separation. Analogous methods gave the corresponding 4-O-methylgalloyl esters of arbutin. Structures were assigned on the basis of analytical and spectroscopic evidence combined with paper chromatographic behaviour, and the identity of the synthetic 2-O-galloyl ester with that derived[1] from *Arctostaphylos uva ursi* was confirmed. In the case of 2-O-(4'-O-methylgalloyl)arbutin (Id) final confirmation of its structure was also derived by an unambiguous synthesis of its hexa-acetate by condensation of 3,5-diacetyl-4-O-methylgalloyl chloride and O-acetylquinol-3,4,6-triacetyl-β-D-glucoside.

Methods to distinguish between 2- and 3-galloyl substitution of the arbutin nucleus were the behaviour on treatment with base[1,6] ($NaHCO_3$ or ammonia) and NMR spectroscopy. Previous work[6] has shown 2-acyl derivatives of arbutin to undergo a facile rearrangement under base catalysis to give the corresponding 6-acyl derivatives; the migration proceeds via an intermediate which was assigned the 3- or 4-acyl structure. The synthetic 3-galloylarbutin rearranged to give a product chromatographically indistinguishable from 6-galloylarbutin (Ia).[1] No intermediate could be detected in this migration. Synthetic and natural 2-O-galloylarbutin also rearranged to give 6-O-galloylarbutin, via an intermediate which had identical paper chromatographic characteristics to 3-O-galloylarbutin. These observations and analogous ones with the 4-O-methylgalloyl esters support therefore a $2 \rightarrow 3 \rightarrow 6$ migration sequence.[1]

A distinctive feature in the NMR spectrum of arbutin in D_2O is the AB quartet of the aromatic protons (Table). In the 3-galloyl esters (1e and 1f) this feature is still

TABLE 1. SOME DERIVATIVES OF ARBUTIN; PMR PATTERN OF THE AROMATIC REGION (τ VALUES) *D_2O

Compound	Hydroquinone protons	Galloyl protons
Arbutin*	2·92, 3·15 (q)	—
Ic*	3·15 (s)	2·75 (s)
Id*	3·15 (s)	2·82 (s)
Ie*	2·95, 3·05 (q)	2·70 (s)
If*	2·95, 3·05 (q)	2·75 (s)
Va*	3·08 (s)	2·83, 2·88 (s)
Vb*	3·08 (s)	2·88, 2·98 (s)

present in the spectrum. However in the case of the 2-galloyl and 2,3-bisgalloyl derivatives (Ic, Id, Va, Vb) the shielding effect of the adjacent aromatic acyl group causes a small shift upfield of one pair of protons and collapse of the AB quartet to a singlet. Similar conformational arguments to those employed in previous work[7] may be used to explain this effect.

All attempts to convert either of the esters (Ic or Id) to compounds of the bergenin type have proved unsuccessful. Under hydrolytic (acid) conditions all the products obtained are those expected from normal hydrolysis of molecules of this type, (hydroquinone, gallic or 4-O-methylgallic acid and glucose). Under oxidative conditions the products vary according to the oxidant used. Manganese dioxide, silver oxide and chloranil had little or no effect. Ferric chloride gave a small yield of *p*-benzoquinone and products tentatively identified paper chromatographically as 2-O-galloyl-D-glucose and the corresponding 4-O-methyl-galloyl ester. Oxidants requiring basic conditions (e.g. potassium ferricyanide, hydrogen peroxide) gave complex results since under the conditions employed to achieve oxidation facile acyl migration also occurred. Potassium iodate transformed 2-galloylarbutin to products of undefined structure; *p*-benzoquinone was however not liberated in the reaction. Further attempts to bring about a biogenetic type synthesis of bergenin are under investigation.

EXPERIMENTAL

All m.ps are uncorrected. PMR measurements were carried out in D_2O or $CDCl_3$ using a Varian A-60 machine. Mass spectra were obtained in an A.E.I. M.S/9 instrument; samples were introduced directly into the ionising beam on a probe. Bergenin was isolated from the roots and rhizomes of *Bergenia crassifolia* as described[3] with minor modifications to the chromatographic procedure. Paper chromatography was carried out using Whatman No. 1 paper in the solvent systems A, 6% aqueous AcOH, and B, butan-2-ol–AcOH–water (14:1:5) at 20 ± 3°. Arbutin and arbutin derivatives were detected by their blue colorations when sprayed with a 1% methanolic soln of 2,6-dibromobenzoquinone-4-chloromide (Gibbs reagent[8]) followed by a sat. soln of $NaHCO_3$ aq. Galloyl esters were revealed by their absorption or violet fluorescence under UV light, by the general vic-dihydroxyphenol spray of ferric chloride—potassium ferricyanide[9] (0·2% w/v solns; 1:1) and by a spray of a saturated soln of potassium iodate.[10]

Tri-O-methyl and penta-O-methylbergenin. To a refluxing suspension of di-O-methylbergenin (1·1 g) in acetone (30 ml) and MeI (17 ml) Ag_2O (2·8 g) was added over 3 hr. After a further hr, the soln was cooled and filtered and the Ag residues extracted with hot acetone. The combined filtrate and washings were evaporated to a gum which was separated by TLC on silica-gel using EtOAc as developing solvent. Two bands were located under UV light (R_f 0·3 to 0·35 and 0·8–0·9) and were cut out and eluted with acetone. Crystallization of the former from MeOH gave tri-O-methylbergenin (0·3 g), m.p. 238–239°, (lit. m.p. 240–242°). (Found: C, 55·0; H, 6·3. Calc. for $C_{17}H_{22}O_9$: C, 55·1; H, 6·0%), ν_{max} (Nujol) at 3200, 1750 cm^{-1}. Crystallization of the second band from acetone gave penta-O-methyl bergenin (0·45 g), m.p. 156–157°, (lit. m.p. 156°). (Found: C, 57·2; H, 6·4. Calc. for $C_{19}H_{26}O_9$: C, 57·3; H, 6·5%). ν_{max} (Nujol) at 1733 cm^{-1}.

Quinol-4,6-benzylidene-β-D-glucoside. A mixture of arbutin (10 g), freshly distilled benzaldehyde (40 g) and powdered $ZnCl_2$ (10·5 g) was shaken continuously for 36 hr and then poured with vigorous stirring into ice-water (250 ml). After ½ hr the water was decanted and the product triturated with light petroleum (b.p. 40–60°) before filtration. Recrystallization from EtOH–water (1:1) gave *quinol-4,6-benzylidene-β-D-glucoside* (5·2 g) as needles, m.p. 252°. (Found: C, 63·6; H, 5·6. $C_{19}H_{20}O_7$ requires: C, 63·3; H, 5·5%), ν_{max} (Nujol) at 3400, 1525 cm^{-1}. The compound gave a deep blue colour with Gibbs reagent. The *triacetate* crystallized from EtOH as needles, m.p. 196–197°. (Found: C, 61·8; H, 5·2. $C_{25}H_{26}O_{10}$ requires: C, 61·7; H, 5·4%).

p-Benzyloxyphenyl-4,6-benzylidene-β-D-glucoside. Quinol-4,6-benzylidene-β-D-glucoside (31·0 g) was dissolved in MeOH (100 ml) and ethanolic KOH aq (5 g in 60 ml EtOH and 40 ml water) followed by benzyl chloride (10 ml) added to the soln under reflux. After ½ hr the soln was cooled and the product collected. Recrystallization from EtOH gave *the glucoside* as needles (18·2 g), m.p. 179–180°. (Found: C, 68·3; H, 6·1. $C_{26}H_{26}O_7 \cdot \frac{1}{2} C_2H_5OH$ requires: C, 68·5; H, 6·1%). The *diacetate* crystallized from EtOH as needles, m.p. 173–174°. (Found: C, 67·2; H, 5·5. $C_{30}H_{30}O_9$ requires: C, 67·4; H, 5·6%).

Methyl 3,5-di-O-benzyl-4-O-methyl gallate. Methyl 4-O-methylgallate (25 g) was added to a vigorously stirred mixture of K_2CO_3 (65·0 g), KI (17 g) and acetophenone (200 ml) at 100°, in an atmosphere of CO_2.

The temp was raised to 150° and during 1 hr benzyl chloride (45 ml) added. After a further 4 hr the mixture was steam distilled to remove acetophenone and the residual soln cooled and extracted with benzene. Removal of the benzene and crystallization from benzene–light petroleum (b.p. 40–60°) gave the *ester* (29·0 g) as needles, m.p. 118–119°. (Found: C, 72·9; H, 5·7. $C_{23}H_{22}O_5$ requires: C, 73·0; H, 5·8%), ν_{max} at 1700 cm^{-1}. The corresponding *acid* prepared by saponification gave, after crystallization from EtOAc–light petroleum (b.p. 40–60°), prisms, m.p. 166°. (Found: C, 72·5; H, 5·4. $C_{22}H_{20}O_5$ requires: C, 72·5; H, 5·5%), ν_{max} at 1665 cm^{-1}. The *acid chloride*, prepared using $SOCl_2$, crystallized from benzene as needles, m.p. 124°. (Found: C, 69·4; H, 5·1. Cl, 9·4. $C_{22}H_{19}O_4Cl$ requires: C, 69·1; H, 5·0; Cl, 9·2%), ν_{max} at 1750 cm^{-1}.

Preparation of 2-O-*galloylarbutin*, 3-O-*galloylarbutin and* 2,3-*di*-O-*galloylarbutin*. Tri-O-benzylgalloyl chloride (7·8 g) and *p*-benzyloxyphenyl-4,6-benzylidene-β-D-glucoside (7·0 g) were dissolved in dry pyridine (50 ml) and left at 20° for 5 days. The reaction mixture was diluted with EtOAc (250 ml), washed with HCl (5N, 3X and 0·05 N, 3X) and dried (Na_2SO_4). The mixture was hydrogenated over Pd–C (10%, 0·5 g, 3X) until uptake of H_2 ceased and then subject to counter-current distribution between EtOAc and water (phase volume 50 cc, 1 : 1, 50 transfers). The contents of every third tube were analysed by chromatography in solvent system B and using Gibbs reagent as spray. On the basis of this analysis tubes 1–6, 7–13, 19–25, 26–33 and 39–41 were grouped together. Tubes 1–6 gave, after removal of the solvent and crystallization from acetone, arbutin, m.p. and mixed m.p. 194–195°. Tubes 7–13 similarly treated gave, after crystallization from acetone–benzene and finally water, 2-O-galloylarbutin as needles (0·25 g), m.p. 165–167° (lit. m.p. 164–166°). (Found: C, 52·7; H, 5·2. Calc. for $C_{19}H_{20}O_{11}\cdot\frac{1}{2}H_2O$: C, 52·6; H, 4·9%), ν_{max} at 3300, 1690 cm^{-1}, R_f(A) 0·69, R_f(B), 0·57.

Tubes 19–25 treated as above gave 3-O-*galloylarbutin* crystallizing in small needles (0·4 g) from acetone–benzene, m.p. 145–146°. (Found: C, 53·6; H, 5·0. $C_{19}H_{20}O_{11}$ requires: C, 53·7; G, 4·7%), ν_{max} at 3300, 1690 cm^{-1}, R_f(A) 0·56, R_f(B) 0·54.

Tubes 39–41 treated as above gave 2,3-*di*-O-*galloylarbutin* crystallizing as prisms (0·65 g) from acetone–benzene, and finally water, m.p. 208–210°. (Found: C, 50·6; H, 5·0. $C_{26}H_{24}O_{15}\cdot 2H_2O$ requires: C, 51·0; H, 4·6%), ν_{max} at 3300, 1690 cm^{-1}, R_f(A) 0·52, R_f(B) 0·62.

Preparation of 2-O-(4-O-*methylgalloyl*)*arbutin*, 3-O-(4-O-*methylgalloyl*)*arbutin and* 2,3-*di*-O-(4-O-*methylgalloyl*)*arbutin*. Reaction of 3,5-di-O-benzyl-4-O-methylgalloyl chloride (8·1 g) and *p*-benzyloxyphenyl-4,6-benzylidene-β-D-glucoside (7·9 g) was achieved as in the corresponding reaction above. Isolation of the products, hydrogenation and counter-current distribution was carried out as above. Tubes 1–9 gave arbutin, m.p. and mixed m.p. 194–195°. Tubes 10–35 gave, after crystallization from acetone, 2-O-(4′-O-*methylgalloyl*)*arbutin* (0·4 g) as prisms, m.p. 236–237°. (Found: C, 54·7; H, 5·3. $C_{20}H_{22}O_{11}$ requires: C, 54·8; H, 5·0%), ν_{max} at 3400, 3250, 1700 cm^{-1}, R_f(A) 0·80, R_f(B) 0·79. The *hexa-acetate* crystallized as needles from EtOH, m.p. 74–76°. (Found: C, 55·7; H, 5·2. $C_{32}H_{34}O_{17}$ requires: C, 55·7; H, 4·9%), ν_{max} at 1760, 1750 cm^{-1}, PMR spectrum in $CDCl_3$ showed absorption at τ, 2·40 (2H); 3·05 (4H), 4·60, 4·66, 4·75, 4·85, 4·95, 5·80 (7 protons of glucose residue); 6·13 (3H); 7·67, 7·75, 7·94, 7·97, 8·05 (18 protons, —CO·CH_3).

Tubes 47–50 on evaporation gave a brown gum which was dissolved in acetone and treated with light petroleum (b.p. 40–60°). After 2 hr at room temp the mother liquor was removed, evaporated to smaller volume and treated with benzene. 2,3-*Bis*-(4′-O-*methylgalloyl*)*arbutin* was obtained as prisms (0·4 g), m.p. 175–176°. (Found: C, 55·9; H, 5·0. $C_{28}H_{28}O_{15}$ requires: C, 55·6; H, 4·6%), ν_{max} at 3300, 1700 cm^{-1}. The *hepta-acetate* crystallized from EtOH as small needles, m.p. 88–89°. (Found: C, 56·2; H, 5·0. $C_{42}H_{42}O_{22}$ requires: C, 56·1; H, 4·7%), ν_{max} at 1765, 1750 cm^{-1}. The PMR spectrum in $CDCl_3$ showed absorption at τ, 2·45 (4H); 3·05 (4H); 6·17 (6H, OMe); 7·70, 7·78, 7·86, 7·94, 8·05 (21H, CO·CH_3).

The residue and mother liquor from tubes 47–50 was resubjected to counter-current distribution between EtOAc and water (40 transfers). Tubes 21–30 on evaporation and crystallization of the residue from acetone–benzene and finally water gave 3-O-(4′-O-*methylgalloyl*)*arbutin* as small prisms, m.p. 180–182°. (Found: C, 53·9; H, 5·1. $C_{20}H_{22}O_{11}\cdot H_2O$ requires: C, 53·7; H, 5·1%), ν_{max} at 3350, 1700 cm^{-1}.

Hexa-acetate of 2-O-(4′-O-*methylgalloyl*)*arbutin*. A soln of O-acetylquinol-3,4,6-triacetyl-β-D-glucoside[6] (0·1 g) and 3,5-diacetyl-4-O-methylgalloyl chloride (0·4 g) in pyridine (25 ml) was kept at 20° for 48 hr and then poured into EtOAc (150 ml). The soln was extracted with 2N-HCl (3 × 100 ml) and water (2 × 100 ml), dried (Na_2SO_4) and evaporated to a gum. The latter was dissolved in benzene (10 ml) and filtered through alumina (10 g). Evaporation of the eluate and crystallization from EtOH gave the hexa-acetate, m.p. and mixed m.p. 75–76°. The IR spectrum of the hexa-acetate formed as above was identical with that produced as indicated earlier.

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