Monatshefte für Chemie 111, 469—473 (1980)

Monatshefte für Chemie

The Synthesis of 2- and 6-O-*p*-Coumaroyl and 6-O-*p*-Hydroxybenzoyl Arbutin Derivatives

Manju Varma*, Rajender S. Varma, and **Madhanam R. Parthasarathy***

Department of Chemistry, University of Delhi, Delhi-110007, India

(Received 21 May 1979. Accepted 29 June 1979)

The Synthesis of 2 and 6-O-*p*-Coumaroyl and 6-O-*p*-hydroxybenzoyl derivatives of arbutin isolated from the leaves of *Grevillea robusta* and *Hakea saligna* is described.

(Keywords: Arbutin; 2- and 6-O-p-Coumaroyl arbutin; Grevillea robusta; Hakea saligna; 6-O-p-Hydroxybenzol arbutin; Proteaceae)

Synthese von 2- und 6-O-p-Cumaroyl- und 6-O-p-Hydroxybenzoyl-Derivaten des Arbutins

Die Synthese der im Titel genannten Derivate von Arbutin, das aus den Blättern von *Grevillea robusta* und *Hakea saligna* isoliert wurde, ist beschrieben.

Introduction

In an earlier paper[1] the isolation and identification of two coumaroyl and one benzoyl ester of the phenolic glucoside arbutin (**1a, 1b, 1c**) from the leaves of *Grevillea robusta* and *Hakea saligna* was described. During a programme of studies of the phenolic constituents of the *Proteaceae* members the structure of these compounds has been confirmed by the synthesis of their acetyl derivatives. The present communication deals with these syntheses and their spectral data (PMR and IR).

Results and Discussion

Synthesis of 6-O-p-Coumaroylarbutin pentaacetate (**1f**)

This was attempted by a method analogous to the synthesis of 6-caffeylarbutin hexaacetate[2]. Tritylation of arbutin (**1**) with triphenylchloromethane in the presence of pyridine followed by acetylation

0026-9247/80/0111/0469/$ 01.00

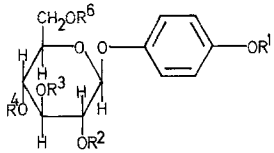
yielded 0-acetylquinol-2,3,4-tri-0-acetyl-6-0-trityl-β-*D*-glucoside (**1 d**). Detritylation of the product with a saturated solution of HBr in glacial acetic acid yielded 0-acetylquinol-2,3,4-tri-0-acetyl-β-*D*-glucoside (**1 e**). The condensation of **1 e** with *p*-acetoxycinnamoyl chloride in chloroform in the presence of pyridine afforded the product **1 f** with on direct comparison with the natural acetate proved its identity.

Synthesis 6-0-p-acetoxy benzoyl arbutin tetraacetate (**1 g**)

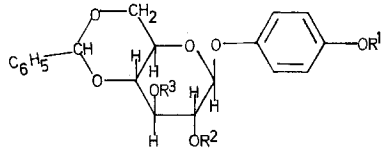
1 e is condensed with *p*-acetoxy benzoyl chloride under similar conditions used for **1 f** and the resulting product **1 g** on comparison agreed with the acetate of the natural sample in all respects.

Synthesis of 2-0-p-Coumaroyl arbutin pentaacetate (**1 h**)

A method similar to the one used for 2-0-galloyl arbutin[3] was used. Arbutin (**1**) is condensed with freshly distilled benzaldehyde in presence of fused zinc chloride to give quinol-4-6-benzylidene-β-*D*-glucoside (**2**). Subsequent benzylation with benzyl chloride in presence of ethanolic KOH afforded *p*-benzoyloxyphenyl-4,6-benzylidene-β-*D*-glucoside (**2 a**). Condensation of **2 a** with *p*-acetoxycinnamoyl chloride in the



1 $R^1 = R^2 = R^3 = R^4 = R^6 = H$
1 a $R^1 = R^2 = R^3 = R^4 = H$, $R^6 = CO—CH=CH—C_6H_4(OH)$-*p*
1 b $R^1 = R^3 = R^4 = R^6 = H$, $R^2 = CO—CH=CH—C_6H_4(OH)$-*p*
1 c $R^1 = R^2 = R^3 = R^4 = H$, $R^6 = CO—C_6H_4(OH)$-*p*
1 d $R^1 = R^2 = R^3 = R^4 = COCH_3$, $R^6 = CPh_3$
1 e $R^1 = R^2 = R^3 = R^4 = COCH_3$, $R^6 = H$
1 f $R^1 = R^2 = R^3 = R^4 = COCH_3$ $R^6 = CO—CH=CH—C_6H_4(OCOCH_3)$-*p*
1 g $R^1 = R^2 = R^3 = R^4 = COCH_3$ $R^6 = CO—C_6H_4(OCO—CH_3)$-*p*
1 h $R^1 = R^3 = R^4 = R^6 = COCH_3$ $R^2 = CO—CH=CH—C_6H_4(OCOCH_3)$-*p*



2 $R^1 = R^2 = R^3 = H$
2 a $R^1 = CH_2C_6H_5$, $R^2 = R^3 = H$

presence of pyridine followed by hydrogenation over Pd—C and acetylation yielded a mixture which is subjected to preparative TLC. One of the products (**1 h**) isolated (30% yield) is found to be identical with the acetate of natural glucoside (**1 b**).

Experimental

PMR spectra (δ/ppm) were determined on a Varian 60 MHz instrument using $CDCl_3$ as solvent and TMS as internal standard and IR spectra recorded as KBr discs unless otherwise mentioned on a Perkin-Elmer infracord spectrometer.

0-acetylquinol-2,3,4-tri-0-acetyl-6-0-(p-acetoxy cinnamoyl)-β-D-glucoside (**1 f**)

(a) *0-Acetylquinol-2,3,4-tri-0-acetyl-6-0-trityl-β-D-glucoside* (**1 d**)

Arbutin (1 g) and triphenylchloromethane (1 g) were dissolved in dry pyridine (10 ml) and the solution stirred at room temperature for 24–30 h. Acetic anhydride (10 ml) was added and the mixture left overnight. The mixture was poured with stirring into ice-water (100 ml) and the product was filtered off. The trityl derivative was recrystallized from ethanol (1,4 g) m. p. 195–196° (lit. m. p. 197–198°).

IR: 1739, 1592, 1538, 1493, 1447, 1429, 1364, 1322, 1178, 1055, 1010, 981, 942, 920, 840, 781, 768, 746, 703 and 694 cm^{-1}.

PMR: 7.53–7.15 (m, 19 H, *Ar*-H), 5.44–5.26 (m, sugar protons), 3.41 (d, 2 H, $—CH_2—$), 2.39 (S, 3 H, *Ar*-$COCH_3$), 2.16 (S, 3 H, —O—$COCH_3$), 2.13 (S, 3 H, —O—$COCH_3$), 1.82 (S, 3 H, —O—$COCH_3$).

(b) *O-Acetylquinol-2,3,4-tri-0-acetyl-β-D-glucoside* (**1 e**)

To the solution of trityl ether **1 d** (1 g) in acetic acid (5 ml) at 10° was added a saturated solution of dry HBr in glacial acetic acid (1.5 ml). The precipitated trityl bromide was filtered off and the filtrate poured into ice-water (50 ml) and extracted with $CHCl_3$ (3 × 50 ml). The chloroform layer was washed with water, dried and evaporated on a rotary vacuum evaporator maintaining the temperature of the bath at 30 °C. The gummy mass obtained was purified by precipitation from ethanol with water and then recrystallized from ethanol giving needle shaped crystals (500 mg) m.p. 146–170° (lit. m.p. 147–180°).

IR: 3571, 1745, 1595, 1493, 1429, 1366, 1250, 1170, 1090, 1010, 985, 902, 861 and 787 cm^{-1}.

PMR: 7.03 (S, 4 H, *Ar*-H), 5.26–5.16 (m, sugar protons), 4.31–4.18 (m, sugar protons), 2.29 (S, 3 H, *Ar*-$COCH_3$), 2.03 (S, 9 H, —O—$COCH_3$).

(c) *O-Acetylquinol-2,3,4-tri-0-acetyl-6-0-(p-acetoxy cinnamoyl)-β-D-glucoside* (**1 f**)

The product from the previous step (b) (180 mg) was disolved in $CHCl_3$ (4,5 ml) containing pyridine (1 ml). To this was added a solution of *p*-acetoxycinnamoyl chloride (150 mg) in $CHCl_3$ (1,8 ml), dropwise, in a duration of 1 h with constant shaking. The mixture was left at the room temp. for 24 h. The solution was then diluted with chloroform (15 ml) and the organic layer washed successively with ice-cold 2*N*—HCl (2 × 10 ml), saturated $NaHCO_3$ (2 × 10 ml) and finally with water and dried (Na_2SO_4). $CHCl_3$ was evaporated and the product crystallized from methanol to give 6-0-*p*-coumaroyl arbutin

pentaacetate as colourless needles (100 mg) m.p. 192-193°. Mixed m.p. was undepressed with the acetate of the natural sample.

IR: 1754, 1718, 1634, 1590, 1493, 1312, 1220, 1010, 855, 830 and 690 cm^{-1}.

PMR: 7.68 (d, J = 17 Hz, 1 H, *Ar*-CH=CH—), 7.60 (d, J = 10 Hz, 2 H, *Ar*-H), 7.12 (d, J = 10 Hz, 2 H, *Ar*-H), 7.0 (S, 4 H, *Ar*-H), 6.41 (d, J = 17 Hz, 1 H, *Ar*-CH=CH—), 5.33-4.3 (m, sugar protons), 2.3 (S, 3 H, *Ar*-$COCH_3$), 2.25 (S, 3 H, *Ar*-$COCH_3$), 2.05 (S, 9 H, —CH_2O—$COCH_3$).

6-0-p-acetoxy benzoylarbutin tetraacetate (**1 g**)

O-Acetyl-quinol-2,3,4-tri-0-actyl-β-glucoside (**1 e**) (100 mg) was dissolved in $CHCl_3$ (4 ml) containing Pyridine (0.85 ml). To this was added a solution of *p*-acetoxybenzoyl chloride (125 mg) in $CHCl_3$ (1,5 ml), dropwise, in a duration of 1 h with constant shaking. The mixture was left at room temperature for 24 h and then worked up as in step (c) above. The product crystallized from methanol to give 6-0-*p*-acetoxybenzoyl arbutin tetraacetate as colourless rods (80 mg), m. p. 170-171°. Melting point was not depressed on admixture with the acetate of the natural sample and its identity was further confirmed by CO-TLC and CO-IR.

IR: (Nujol) 1716, 1733, 1613, 1515, 1383, 1263, 1086, 1042, 981, 917, 866, 825, 762 and 714 cm^{-1}.

PMR: 7.96 (d, J = 9 Hz, 2 H), 7.10 (d, J = 9 Hz, 2 H), 6.75 (S, 4 H, *Ar*-H), 4.34-5.12 (m, sugar protons), 2.29 (S, 3 H, *Ar*-$COCH_3$), 2.23 (S, 3 H, *Ar*-$COCH_3$), 2.04 (S, 9 H, —O—$COCH_3$).

2-0-p-coumaroyl arbutin pentaacetate (**1 h**)

(a) *Quinol-4,6-benzylidene-β-D-glucoside* (**2**)

A mixture of arbutin (**1**) (2 g), freshly distilled benzaldehyde (8 g) and powered zinc chloride (2 g) was stirred continuously for 36 h and then poured with vigorous stirring into ice-water (50 ml). It was allowed to stand for 0.5 h. Water was decanted off and the product macerated with light petroleum ether. It was then filtered and crystallized from ethanol: water (1:1) to give **2** (1 g) as colourless needles m. p. 249-250° (lit m. p. 252°). It formed a triacetate with *Py*/Ac_2O in cold; m.p. 193° (lit. m. p. 196-197°).

IR: 3344, 1511, 1456, 1335, 1277, 1110, 980, 833, 781, 749 and 694 cm^{-1}.

PMR: 7.42 (S, 5 H, *Ar*-H), 7.05 (S, 4 H, *Ar*-H), 5.54 (s, 1 H, *Ar*-C**H**), 5.26 and 3.84-3.70 (m, sugar protons), 2.26 (S, 3 H, *Ar*-$COCH_3$), 2.05 (S, 6 H, O—$COCH_3$).

(b) *p-Benzyloxybenzyl-4,6-benzylidene-β-D-glucoside* (**2 a**)

To 1 g of **2** dissolved in methanol (3,5 ml) was added ethanolic KOH (0,2 g in 2 ml of *Et*OH and 1,5 ml H_2O) followed by benzyl chloride (0,35 ml). The reaction mixture was refluxed for 0.5 h, cooled and the product obtained as a solid was filtered. Recrystallization from alcohol gave the glucoside as needles (0.9 g) m.p. 176-177° (lit. m.p. 179-180°). **2 a** (50 mg) formed a diacetate with *Py*/Ac_2O which crystallized from alcohol as needles (42 mg) m.p. 175° (lit. m.p. 173-174°).

IR: 3333, 1511, 1456, 1335, 1299, 1217, 1110, 980, 877, 781, 749 and 694 cm^{-1}.

PMR: 7.45 (S, 10 H, *Ar*-H), 6.98 (S, 4 H, *Ar*-**H**), 5.59 (S, 1 H, *Ar*-C**H**), 5.06 (S, 2 H, *Ar*-CH_2), 3.71 (m, sugar protons), 2.06 (S, 6 H, O—$COCH_3$).

(c) *2-0-p-coumaroyl arbutin pentaacetate* (**1 h**)

p-Acetoxycinnamoyl/chloride (1.2 g) and **2 a** (0.85 g) were dissolved in dry pyridine and left at room temp. for 5 days. The reaction mixture was diluted with ethyl acetate (30 ml), washed with HCl (5*N* and 0,05*N*, 3 × each) and dried (Na_2SO_4). The mixture was hydrogenated over Pd—C (10% 0.05 g) until uptake of H_2 slowed. It was filtered from catalyst and the solvent evaporated. The crude dried product was then acetylated with Py/Ac_2O in cold. The acetate was worked up in a usual manner. The acetylated product was separated by preparative TLC in the solvent system (10% *EtOAc* in C_6H_6) and the band corresponding to the acetate of the natural compound **1 b** was cut and eluated with chloroform to afford the required product as a solid m.p. 136–137° (25 mg). The mixed melting point with the acetate of the natural compound was undepressed.

IR: 1748, 1714, 1664, 1600, 1502, 1368, 1220, 1185 and 850 cm^{-1}.

PMR: 6.97 (S, 4 H, *Ar*-H), 6.80 (d, J = 10 Hz, 2 H, *Ar*-H), 6.68 (d, J = 17 Hz, 1 H, —CH=CH—), 6.32 (d, J = 10 Hz, 2 H, *Ar*-H), 6.16 (d, J = 17 Hz, 1 H, —CH=CH—), 4.31-5.23 (m, sugar protons), 2.30 (S, 3 H, *Ar*-$COCH_3$), 2.16 (S, 3 H, *Ar*-$COCH_3$), 2.01 (S, 9 H, —O—$COCH_3$).

Acknowledgement

One of the authors (M. V.) is grateful to the CSIR, New Delhi, for a research fellowship.

References

[1] *M. Varma, R. S. Varma*, and *M. R. Parthasarathy*, Phytochemistry **16**, 793 (1977).

[2] *G. Britton, E. Haslam*, and *M. O. Naumann*, J. Chem. Soc. Suppl. **I**, 5649 (1964).

[3] *E. Haslam*, Tetrahedron **24**, 4015 (1968).