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The structure of bergenin*

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ABSTRACT

X-Ray analysis of the 3,4,8,10,11-penta-acetate (**3**) of bergenin has confirmed the earlier structural assignments.

INTRODUCTION

Bergenin (**1**) has been isolated from the roots of *Bergenia crassifolia*[1,2] and *purpurascens*[3] and *Casesalpinia digyna*[4], from the bark of *Corylopsis spicata*[5] and *Mallotus japonicus*[6], and from the heartwood of *Shorea leprosula*[7] and *Macaranga peltata*[8]. Extraction of the bark of *Macaranga peltata*, a small tree commonly found in Indian forests, gave[8], in addition to **1**,the di-*O*-methyl derivative **2**. A gum powder of this tree has been used in Indian medicine for the treatment of venereal diseases[8,9] and other medicinal applications have been reported[3,6,10].

The first structures proposed[2,11] for **1** were revised independently by Hay and Haynes[12] and by Posternak and Dürr[13]. In order to clarify the structure[8,14,15], an attempt was made to obtain crystalline material suitable for X-ray analysis[16]. A straightforward synthesis of this type of *C*-glycosylarene was developed[16] and has been reported[17].

RESULTS AND DISCUSSION

The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**5**) with 4-*O*-methylgallic acid methyl ester (**6**) in the presence of methanolic sodium methoxide gave[12] 1.6% of a product that had physical data in agreement with those of natural bergenin (**1**). The n.m.r. data of **1**, its penta-acetate **3**, and **2**, and its tri-acetate **4**, were taken as further proof of the structure assigned[8] previously. However, the low-yielding synthesis and the relatively high field ^{1}H-n.m.r. shift (δ 4.29) observed for the resonance of H-4a of **3** did not rule out isomeric structures[14,15] which can be formed readily from the precursors[16]. Therefore, **2** was synthesised by an independent route[15]. Intramolecular *C*-glucosylation of the trichloroacetimidate **7** followed by hydrogenolysis and acetylation gave a major product that had ^{1}H-n.m.r. data much closer to expectations

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[*] Aryl *C*-Glycosides, Part 3. For Parts 1 and 2, see R. R. Schmidt and W. Frick,*Tetrahedron*, 44 (1988) 7163–7169; *Liebigs Ann. Chem.*, (1989) 565–570.
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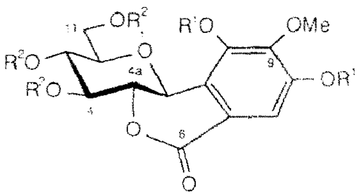
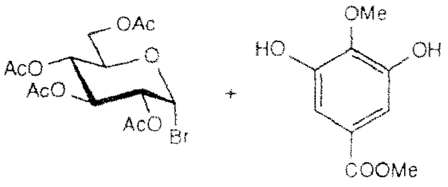
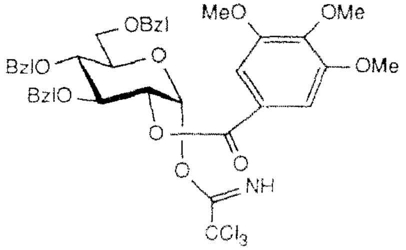


1 R^1 = R^2 = H
2 R^1 = Me, R^2 = H
3 R^1 = R^2 = Ac
4 R^1 = Me, R^2 = Ac



5 **6**



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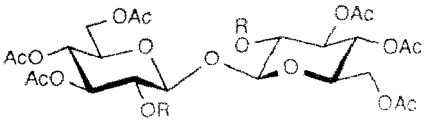

8 R = 3,4,5-Trimethoxybenzoyl

for the structure proposed for bergenin. However, the mass spectrum of this material indicated[16] a mass of 982 (and not of 482), in agreement with the formation of the trehalose derivative **8**. This assignment is also supported by the ^{1}H- and ^{13}C-n.m.r. data, the elemental analysis, and independent synthesis[14,16,17*].

For the unequivocal assignment of the bergenin structure, the synthesis described by Hay and Haynes[12] was repeated and a low yield of a compound with physical data identical to those of the natural product was obtained. Treatment with acetic anhydride–pyridine then furnished **3**, single crystals of which were suitable for X-ray analysis (see Experimental).

The atomic co-ordinates, and selected bond lengths, bond angles, and torsion angles, are listed in Tables I and II. The molecular structure including the numbering scheme is shown in Fig. 1. Thus, the X-ray investigation confirmed the structure **1** proposed[12,13] for bergenin. The bond lengths and the bond angles found for the sugar moiety [Table II, (*a*) and (*b*)] are typical[18]. The torsion angles [Table II, (*c*)] indicate that the glucopyranose moiety exhibits only small deviations from an ideal chair conformation [$^{C\text{-}5}C_{C\text{-}24}$]. The annellated δ-lactone ring possesses the expected half-chair conformation [$^{C\text{-}11}H_{O\text{-}8}$]. The O=C–O–C and also the C–O–C–H torsion angles for the acetoxy groups attached to the sugar moiety were ~0°; but, in the lactone moiety, they were +160.8° (4) [C-11–O-8–C-12–O-9] and –63.3° (3) [H-11A–C-11–O-8–C-12], respec-

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* We thank Professor O. R. Martin (SUNY Binghampton) who also suggested these assignments.

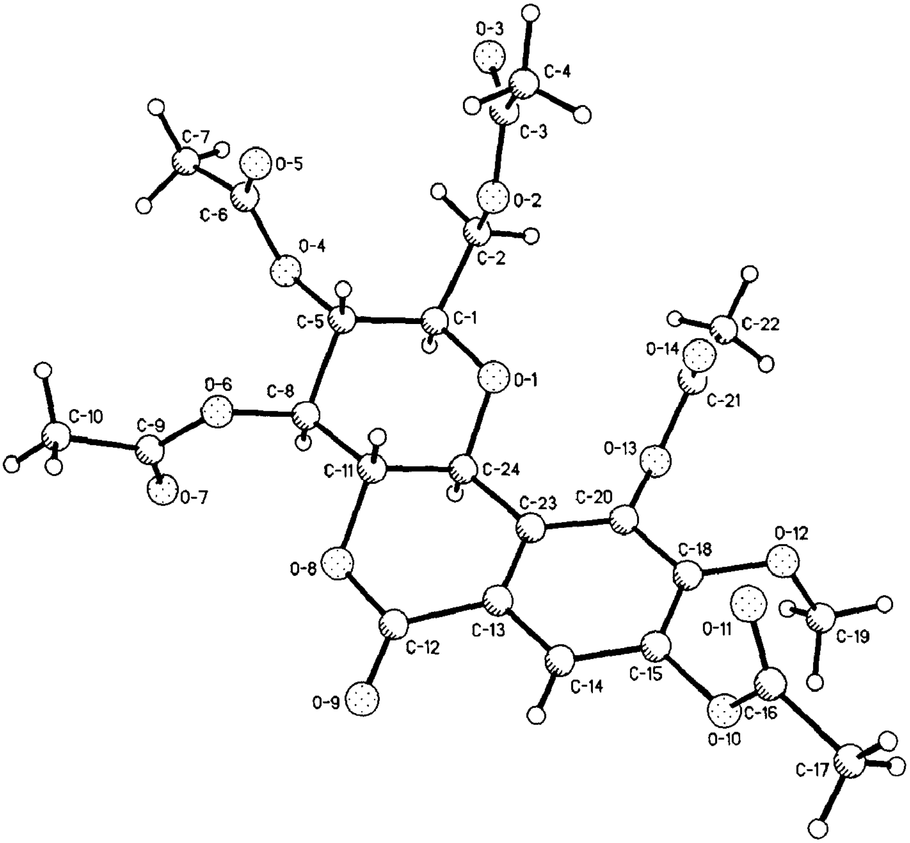

Fig. 1. Structure and numbering of 3,4,8,10,11-penta-*O*-acetylbergenin.

tively. Thus, the chemical shift (δ 4.29) of the resonance for H-4a in **3** is due to the unusual conformation of the attached cabonyloxy moiety which is part of the tricyclic system. This difference in the location of the carbonyl group relative to H-4a influences dramatically the anisotropy effect of the carbonyl group, thus leading to a relative upfield shift ($\sim$ 1 p.p.m.) of the resonance for H-4a. The chemoselective synthesis[17] of **2** and **4** confirmed the structural assignments.

EXPERIMENTAL

General. — The ^{1}H-n.m.r. spectra (internal Me_4Si) were recorded with a Bruker WM 250 spectrometer. I.r. spectra (KBr) were recorded with a Perkin–Elmer 237 spectrophotometer. Melting points are uncorrected. Column chromatography was carried out on silica gel (Merck 70–230 mesh ASTM, and 230–400 mesh for flash chromatography under normal pressure). Melting points are uncorrected.

*3,4,8,10,11-Penta-*O*-acetylbergenin* (**3**). — Bergenin (**1**; 250 mg, 1.6% from **5**), obtained[12] from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**5**; 20 g, 49 mmol)

TABLE I

Atomic co-ordinates for **3** with estimated standard deviations in parentheses.

Atom	x	y	z	U_{eq}
O-1	8715 (3)	3120	9201 (2)	56 (1)
C-1	8131 (5)	2636 (4)	8191 (3)	59 (1)
C-2	8566 (7)	3331 (5)	7256 (5)	84 (2)
O-2	7999 (5)	4352 (4)	7468 (3)	98 (2)
C-3	7799 (9)	5015 (7)	6708 (6)	120 (3)
O-3	7892 (10)	4770 (7)	5719 (5)	206 (4)
C-4	7240 (13)	6013 (7)	7088 (7)	181 (5)
C-5	6451 (5)	2507 (4)	8252 (3)	60 (1)
O-4	5906 (4)	1942 (4)	7270 (3)	84 (1)
C-6	4885 (8)	2414 (9)	6599 (5)	113 (3)
O-5	4493 (8)	3288 (7)	6738 (5)	156 (3)
C-7	4333 (8)	1721 (9)	5691 (6)	158 (5)
C-8	6078 (4)	1897 (3)	9292 (3)	53 (1)
O-6	4489 (3)	1834 (3)	9337 (3)	60 (1)
C-9	3871 (5)	892 (4)	9408 (4)	68 (2)
O-7	4578 (4)	108 (3)	9502 (4)	112 (2)
C-10	2217 (5)	950 (5)	9380 (6)	102 (2)
C-11	6733 (4)	2496 (3)	10275 (3)	48 (1)
O-8	6337 (3)	1988 (3)	11309 (2)	58 (1)
C-12	6895 (4)	2422 (4)	12270 (4)	61 (1)
O-9	6342 (3)	2232 (4)	13139 (3)	84 (1)
C-13	8283 (4)	3074 (4)	12192 (3)	55 (1)
C-14	8811 (5)	3589 (4)	13150 (4)	68 (2)
C-15	10148 (5)	4103 (5)	13138 (4)	70 (2)
O-10	10725 (5)	4591 (5)	14112 (3)	106 (2)
C-16	10512 (10)	5607 (8)	14228 (7)	121 (4)
O-11	9818 (8)	6092 (5)	13536 (5)	133 (2)
C-17	11235 (11)	6025 (9)	15258 (7)	199 (6)
C-18	10998 (5)	4091 (4)	12199 (5)	67 (2)
O-12	12338 (3)	4615 (3)	12191 (3)	82 (1)
C-19	13597 (7)	4036 (7)	12597 (8)	129 (3)
C-20	10469 (4)	3565 (3)	11247 (4)	53 (1)
O-13	11384 (3)	3478 (3)	10343 (3)	59 (1)
C-21	11496 (5)	4324 (4)	9666 (4)	64 (2)
O-14	10834 (3)	5106 (3)	9832 (3)	82 (1)
C-22	12535 (6)	4140 (5)	8756 (5)	89 (2)
C-23	9080 (4)	3081 (3)	11208 (3)	51 (1)
C-24	8417 (4)	2547 (3)	10195 (3)	48 (1)

and methyl 4-*O*-methylgallate[19] (**6**; 10 g, 50 mmol), had m.p. 235–237°; lit.[8] m.p. 237°. Treatment[8] of **1** with excess of acetic anhydride in pyridine afforded **3** (340 mg, 83%), which had m.p., ^{1}H-n.m.r. data, and i.r. data as reported. Careful recrystallisation from ethanol afforded crystals for X-ray analysis*.

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* Tables of observed and calculated structure factors, of positional and thermal parameters, and data additional to the Tables are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA|DD|453|*Carbohydr. Res.*, 210 (1991) 71–77.

TABLE II

Selected data[a] for **3** with estimated standard deviations in parentheses

(*a*) *Bond lengths (pm)*

O-1–C-1	143.0 (5)	O-1–C-24	142.7 (5)
C-1–C-2	149.0 (7)	C-1–C-5	151.9 (6)
C-2–O-2	143.0 (8)	O-2–C-3	124.8 (9)
C-3–O-3	122.4 (9)	C-3–C-4	145.4 (13)
C-5–O-4	144.1 (6)	C-5–C-8	151.3 (6)
O-4–C-6	133.4 (8)	C-6–O-5	118.7 (14)
C-6–C-7	146.7 (12)	C-8–O-6	142.9 (4)
C-8–C-11	149.7 (6)	O-6–C-9	133.4 (6)
C-9–O-7	119.1 (7)	C-9–C-10	148.3 (6)
C-11–O-8	145.0 (5)	C-11–C-24	151.8 (5)
O-8–C-12	134.8 (5)	C-12–O-9	119.0 (6)
C-12–C-13	150.4 (6)	C-13–C-14	138.3 (6)
C-13–C-23	139.7 (6)	C-14–C-15	136.8 (7)
C-15–O-10	139.6 (7)	C-15–C-18	137.9 (7)
O-10–C-16	132.4 (12)	C-16–O-11	118.7 (11)
C-16–C-17	146.4 (12)	C-18–O-12	137.7 (6)
C-18–C-20	138.3 (7)	O-12–C-19	141.8 (8)
C-20–O-13	138.4 (5)	C-20–C-23	138.9 (5)
O-13–C-21	135.8 (6)	C-21–O-14	118.6 (6)
C-21–C-22	147.6 (8)	C-23–C-24	148.8 (6)

(*b*) *Bond angles (degrees)*

C-1–O-1–C-24	113.4 (3)	O-1–C-1–C-2	105.6 (4)
O-1–C-1–C-5	109.6 (3)	C-2–C-1–C-5	113.1 (4)
C-1–C-2–O-2	108.0 (4)	C-2–O-2–C-3	122.4 (5)
O-2–C-3–O-3	120.6 (8)	O-2–C-3–C-4	114.5 (6)
O-3–C-3–C-4	124.3 (8)	C-1–C-5–O-4	108.5 (3)
C-1–C-5–C-8	110.5 (3)	O-4–C-5–C-8	108.9 (4)
C-5–O-4–C-6	117.2 (6)	O-4–C-6–O-5	122.9 (7)
O-4–C-6–C-7	111.5 (9)	O-5–C-6–C-7	125.6 (7)
C-5–C-8–O-6	108.4 (3)	C-5–C-8–C-11	106.3 (3)
O-6–C-8–C-11	110.9 (3)	C-8–O-6–C-9	118.1 (4)
O-6–C-9–O-7	123.4 (4)	O-6–C-9–C-10	111.7 (5)
O-7–C-9–C-10	124.9 (5)	C-8–C-11–O-8	109.3 (3)
C-8–C-11–C-24	109.3 (3)	O-8–C-11–C-24	110.6 (3)
C-11–O-8–C-12	116.0 (3)	O-8–C-12–O-9	119.9 (4)
O-8–C-12–C-13	117.0 (4)	O-9–C-12–C-13	122.9 (4)
C-12–C-13–C-14	118.0 (4)	C-12–C-13–C-23	120.6 (4)
C-14–C-13–C-23	121.2 (4)	C-13–C-14–C-15	119.4 (4)
C-14–C-15–O-10	120.0 (4)	C-14–C-15–C-18	121.1 (5)
O-10–C-15–C-18	118.7 (4)	C-15–O-10–C-16	118.5 (5)
O-10–C-16–O-11	121.2 (8)	O-10–C-16–C-17	112.7 (8)
O-11–C-16–C-17	126.1 (10)	C-15–C-18–O-12	120.8 (5)
C-15–C-18–C-20	119.1 (4)	O-12–C-18–C-20	120.0 (4)
C-18–O-12–C-19	115.0 (5)	C-18–C-20–O-13	118.8 (3)
C-18–C-20–C-23	121.3 (4)	O-13–C-20–C-23	119.9 (4)
C-20–O-13–C-21	117.3 (4)	O-13–C-21–O-14	121.7 (4)
O-13–C-21–C-22	111.9 (4)	O-14–C-21–C-22	126.4 (5)
C-13–C-23–C-20	117.7 (4)	C-13–C-23–C-24	118.3 (3)
C-20–C-23–C-24	123.9 (4)	O-1–C-24–C-11	107.2 (3)
O-1–C-24–C-23	110.6 (3)	C-11–C-24–C-23	109.4 (3)

TABLE II (continued)

Selected data[a] for **3** with estimated standard deviations in parentheses

(*c*) *Torsion angles (degrees)*	
O-1–C-1–C-5–C-8	−56.0 (0.5)
C-1–C-5–C-8–C-11	58.3 (0.4)
C-5–C-8–C-11–C-24	−62.3 (0.4)
C-8–C-11–C-24–O-1	63.7 (0.4)
C-1–O-1–C-24–C-11	−61.9 (0.4)
C-24–O-1–C-1–H-1A	−60.5 (0.3)
H-1A–C-1–C-5–H-5A	−175.2 (0.0)
H-8A–C-8–C-11–C-24	56.7 (0.3)
H-11A–C-11–C-24–O-1	−55.2 (0.3)
H-11A–C-11–C-24–C-23	64.9 (0.3)
H-11A–C-11–C-24–H-24A	−174.8 (0.0)
C-12–C-13–C-23–C-24	8.2 (0.6)
C-13–C-23–C-24–C-11	24.3 (0.5)
O-8–C-11–C-24–C-23	−56.0 (0.4)
C-24–C-11–O-8–C-12	57.4 (0.5)
C-11–O-8–C-12–C-13	−23.4 (0.5)
O-8–C-12–C-13–C-23	−10.2 (0.6)
C-8–C-11–O-8–C-12	177.8 (0.3)
O-8–C-11–C-24–O-1	−176.0 (0.3)
C-23–C-13–C-14–C-15	−0.8 (0.7)
C-14–C-13–C-23–C-20	4.2 (0.7)
C-1–O-1–C-24–C-23	178.8 (0.3)
C-12–C-13–C-14–C-15	173.6 (0.5)
C-12–C-13–C-23–C-20	−170.1 (0.4)
C-14–C-13–C-23–C-24	−177.6 (0.4)
C-12–C-13–C-14–H-14A	−4.3 (0.5)
H-5A–C-5–O-4–C-6	−0.8 (0.5)
C-5–O-4–C-6–O-5	5.1 (1.0)
C-8–O-6–C-9–O-7	4.5 (0.7)
H-8A–C-8–O-6–C-9	4.3 (0.4)
C-11–O-8–C-12–O-9	160.8 (0.4)
H-11A–C-11–O-8–C-12	−63.3 (0.3)

[a] The H-atoms are calculated in ideal geometric position and were refined isotropic with fixed thermal parameters.

Crystal data for **3** ($C_{24}H_{26}O_{14}$). — Colourless; crystal size, 0.5 × 0.5 × 0.5 mm; monoclinic, space group $P2_1$; unit-cell dimensions, a = 8.966 (2) Å, b = 12.823 (3) Å, c = 11.895 (4) Å, β = 92.47 (2)°; volume, 1365.4 Å^3; z 2; mol. wt., 538.46; density (calc.), 1.31 g/cm^3; absorption coefficient, 1.0 cm^{-1}; $F(000)$ 564. Data collection: Nicolet P3 diffractometer; Mo-K_α radiation (λ = 0.71073 Å); temperature, 299 K; monochromator highly oriented graphite crystal; 2Θ range, 4.0–52.0; scan type, omega; scan speed, 2.00–29.3°/min in ω; scan range, 1.0°. Background measurement, stationary crystal and stationary counter at the beginning and end of the scan, each for 20% of the total scan time; 3 standard reflections measured every 97 reflections; 2991 reflections collected; 2804 (R_{int} = 1.34%) independent reflections; 2804 [$F > 0\sigma(F)$] observed reflections. Solution and refinement: Nicolet SHELXTL PLUS (Microvax II), direct methods, full-matrix least-squares; quantity minimised, $\Sigma w(F_o - F_c)^2$. Hydrogen atoms, riding model, fixed isotropic U; weighting scheme, $w^{-1} = \sigma^2(F) + 0.0005F^2$; final R indices, $R_F = 7.15\%$ $R_F{}^2 = 6.41\%$; goodness-of-fit, 1.5054; data to parameter ratio, 8.1:1; largest difference peak, 0.29 ($e^-/\text{Å}^3$); LS parameter, 343.

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