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GALLOYLSUCROSES FROM RHUBARBS*

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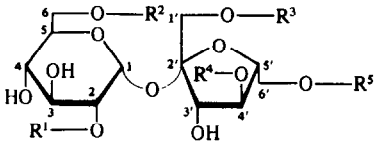
Key Word Index—*Rheum* sp., Polygonaceae, rhubarb; galloylsucroses, gallotannin; gallic acid; sucrose

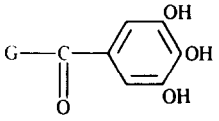
Abstract—Chinese rhubarb yielded a new class of gallotannins having a sucrose core, while North Korean rhubarb was found to contain four gallotannins. On the basis of chemical and spectroscopic evidence, the structures of the gallotannins were established as 6′-*O*-, 4′-*O*-, 6-*O*-, 1′-*O*- and 2-*O*-monogalloylsucrose, respectively

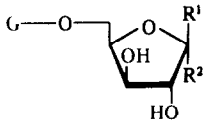
INTRODUCTION

Recent chemical studies have revealed that gallotannins contain in their molecules a variety of alcohol cores, i.e. monosaccharides (D-glucose [2–5], D-hamamelose [6–8], D-fructose [9], D-xylose [Tanaka, T. *et al.*, unpublished data]), polyalcohols (1,5-anhydro-D-glucitol [10], *proto*-quercitol [11, 12], *scyllo*-quercitol [13], quinic acid [12, 14], shikimic acid [12, 15], glycerol [4]), glucosides (methyl-β-D-glycoside [15], mangiferin *C*-glucoside [16], maclurin *C*-glucoside [16], salidroside [17, 18]) etc. Our systematic chemical examination of tannins and related compounds in crude drugs has now led to the isolation of a new class of gallotannins having a sucrose core from two different types of commercial rhubarbs, each produced in China and North Korea. We now report the isolation and structure elucidation of these compounds.



	R^1	R^2	R^3	R^4	R^5
1	H	H	H	H	G
2	H	H	H	G	H
3	H	G	H	H	H
4	H	H	G	H	H
5	G	H	H	H	H





	R^1	R^2
1a	OH·CH_2OH	
1b	OMe	CH_2OH
1c	CH_2OH	OMe

RESULTS AND DISCUSSION

The aqueous acetone extract of the commercial Chinese rhubarb was repeatedly chromatographed over Sephadex LH-20, MCI-gel CHP 20P, Bondapak C_{18}/Porasil B and Fuji-gel ODS G3 with monitoring by HPLC to furnish compounds **1**–**4**, while a similar extraction and chromatography of North Korean rhubarb afforded compounds **1**, **3**–**5**.

Compound **1** showed a blue colouration with ferric chloride reagent. The FAB-MS spectrum exhibited peaks at *m/z* 517 and 495 due to $[M+Na]^+$ and $[M+H]^+$, respectively, together with a characteristic peak at *m/z* 153 indicative of the presence of a galloyl group, which was also supported by the ^1H and ^{13}C NMR data (δ7.24, 2H, *s* and Table 1). The ^{13}C NMR spectrum showed 12 carbon signals due to a polyalcohol moiety, and the presence of two anomeric signals indicated that the polyalcohol was a disaccharide. Acid hydrolysis of **1** with 5% aqueous sulphuric acid to afford gallic acid, glucose and fructose confirmed its constitution. On enzymatic hydrolysis with tannase, **1** yielded gallic acid and a crystalline sugar, which was identified as sucrose by direct comparison with an authentic sample.

Treatment of **1** with 1% aqueous sulphuric acid furnished glucose and a galloylfructose (**1a**). Although the ^1H NMR spectrum of **1a** was duplicated owing to the existence of an equilibrium mixture of α- and β-anomers, no significant lowfield shifts of the sugar methine signals were observed, thus the galloyl group was assumed to be attached to one of the two primary hydroxyl groups in the fructose moiety. In addition, the observation of upfield singlet signals (δ3.54 and 3.66, 2H in total) which were readily assignable to the C-1 methylene protons

* Part 66 in the series 'Tannins and Related Compounds'. For Part 65 see ref [1]. This paper also forms Part XI of 'Studies on Rhubarb (Rhei Rhizoma)'

Table 1 ^{13}C NMR data for galloylsucroses (25 05 MHz, Me_2CO-d_6 + D_2O, TMS as int standard)

	C	Sucrose	1	2	3	4	5
Sucrose	Glucose moiety						
	1	93 0	92 7	93 4	93 1	93 6	90 3
	2	72 3	72.3	72 3	71 6	72 3	74 1
	3	73 7	73 8	73 8	73 8	74 0	71 3
	4	70 5	70 5	70 4	70 8	70 8	70 9
	5	73 7	73 5	73 8	72 5	74 0	73 7
	6	61 5	61 4	61 4	64 4	61 8	61 6
	Fructose moiety						
	1′	62 8	62 9	62 8	63 0	63 8	62 2
	2′	104 7	104 8	105 1	104 8	103 7	105 2
	3′	78 3	77 9	78 2	78 9	78 5	76 6
	4′	74 9	75 8	76 8	75 2	74 0	74 5
	5′	82 8	79 9	82 0	83 0	83 0	82 9
	6′	63 1	66 9	63 1	63 7	62 2	62 7
	Galloyl						
	1″		120 7	120 4	121 2	120 9	120 9
	2″		110 2	110 1	110 0	109 9	110 2
	3″		145 8	146 0	146 0	146 1	145 9
	4″		139 2	139 5	139 1	139 2	139 4
	–COO–		168 0	167 3	167 5	166 9	167 4

suggested that the galloyl group was present at the C-6 hydroxymethyl. On treatment with 0 5% methanolic sulphuric acid, **1** gave methyl-α- and β-glucosides and **1b** and **1c** The ^{1}H NMR spectra of **1b** and **1c** showed, along with methoxyl (δ3.28 in **1b**, δ3 34 in **1c**) and geminally coupled C-1 methylene signals [δ3 64 and 3 70 (each 1H, *d*, *J* = 12 Hz) in **1b**; δ3 65 and 3 80 (each 1H, *d*, *J* = 12 Hz) in **1c**], relatively lowfield two-proton signals [δ4 27 (1H, *dd*, *J* = 6, 12 Hz) and 4 50 (1H, *dd*, *J* = 3, 12 Hz) in **1b**, δ4 32 (1H, *dd*, *J* = 6, 12 Hz) and 4 52 (1H, *dd*, *J* = 3, 12 Hz) in **1c**], assignable to the C-6 methylene protons on the basis of the large coupling constants, indicating clearly that the galloyl group was located at the C-6 position On the basis of these chemical and spectral data, **1** was determined as 6′-*O*-galloylsucrose

Compound **2** showed a similar blue colouration with ferric chloride reagent The FABMS exhibited an $[M+H]^+$ ion peak at *m/z* 495 and a fragment ion peak at *m/z* 153 derived from a galloyl cation, indicating the same constitution as that in **1** Tannase hydrolysis of **2** gave sucrose and gallic acid. The ^{1}H NMR spectrum of **2** was similar to that of **1**, except for the appearance of an extremely lowfield triplet (δ5 40, *J* = 7 Hz) and an isolated doublet (δ4 56, *J* = 7 Hz), the latter being assignable to the C-3 methine proton in the fructose moiety on the basis of its simple coupling pattern Since these signals were shown to be coupled with each other by spin-decoupling experiments, the triplet signal was assigned to the C-4′ methine proton Thus, the galloyl group was presumed to be located at the C-4′ position of the sucrose moiety. This was further supported by ^{13}C NMR analysis, which showed a downfield shift of the C-4′ resonance, as well as the upfield shifts of the neighbouring C-3′ and C-5′ resonances as compared with those of sucrose

Treatment of **2** with 0 5% methanolic sulphuric acid gave a mixture of methyl-α- and β-glucosides and also a mixture of methanolysates (**2a**) The ^{1}H NMR spectrum of **2a** showed methoxyl signals at δ3 32 and 3.40 (3H in total) and galloyl signals at δ7 15 and 7 19 corresponding to two protons. It also showed a lowfield triplet (δ5 26, 5/8H, *J* = 7 Hz) and a double doublet (δ5 21, 3/8H, *J* = 4, 10 Hz), these signals could be assigned to the C-4 methine proton from the fact that they were coupled with the C-3 methine proton signals (δ4.56, *d*, 5/8H, *J* = 7 Hz; δ4 37, *d*, 3/8H, *J* = 10 Hz). Thus, the galloyl group was concluded to be located at the C-4 position in the methyl fructoside moiety, and **2** was established as 4′-*O*-galloylsucrose.

Compounds **3**–**5** showed in the FABMS the same $[M+H]^+$ ion peak (*m/z* 495) as those observed in **1** and **2** In each case, sucrose and gallic acid were detected upon enzymatic hydrolyses with tannase. The ^{13}C NMR spectrum of **3** showed a downfield shift (+2 9 ppm) of the C-6 signal and an upfield shift (−1 2 ppm) of the C-5 signal as compared with those of sucrose, indicating the presence of the galloyl group at the C-6 position In the case of **4**, the carbon resonance due to C-1′ was shifted to the lower field (δ63 8) than that of sucrose, whereas the C-2′ carbon resonance appeared at higher field (δ103.7) Thus, the location of the galloyl group was presumed to be at the C-1′ position In the ^{13}C NMR spectrum of **5**, the C-2 signal was shifted downfield, whereas the neighbouring C-1 and C-3 signals were shifted upfield, suggesting the galloyl group was located at the C-2 position. These observations were further confirmed by hydrolyses of **3**–**5** with 1% aqueous sulphuric acid to furnish 6-*O*-galloylglucose, 1-*O*-galloylfructose and 2-*O*-galloylglucose, respectively Based on the chemical and spectral evidence described above, **3**–**5** were established as 6-*O*-galloylsucrose, 1′-*O*-galloylsucrose and 2-*O*-galloylsucrose, respectively

This is the first example of the isolation of disaccharide gallates and these compounds are classified as a new class of gallotannins

EXPERIMENTAL

Mps uncorr, ^{1}H and ^{13}C NMR 100 and 25 05 MHz, respectively, with TMS as int standard, FDMS 20–22 mA (emit-

ter current) and 3 kV (accelerating voltage); FABMS: 3 kV (accelerating voltage) with H_2O–glycerol as matrix. HPLC: TSK-gel ODS-80TM (150 × 4 mm I.D.) column, MeCN–0.05 M NaH_2PO_4 buffer solution (3 97), UV detector; TLC silica gel and Avecel SF cellulose, spots visualized by $FeCl_3$ (for phenolics) and aniline–hydrogen-phthalate or anisaldehyde–H_2SO_4 (for sugars) reagents. CC Sephadex LH-20 (25-100 mμ, Pharmacia), MCI-gel CHP 20P (75–150 mμ, Mitsubishi), Bondapak C_{18}/Porasil B (waters) and Fuji-gel ODS G3 (43–65 mμ, Fujigel Hanbai).

Plant materials The *Rheum* species are known to be susceptible to mutual hybridization, and their taxonomical classification was therefore not fully made. The Chinese rhubarb (Chinese commercial name. Chong-Gi-Huang) was purchased from a market in Hong Kong and from its appearance and chemical composition seemed to be related to *Rheum palmatum*, while the North Korean rhubarb (Korean commercial name Cho-Seon-Dae-Hwang) was presumed to be *R coreanum*

Extraction and isolation (i) Chinese rhubarb (3.2 kg) was powdered and extracted with 80% aq. Me_2CO at room temp. The extract, after removal of the solvent by evapn, was subjected to chromatography over Sephadex LH-20 with H_2O containing increasing amounts of MeOH (1:0–0·1) to give six fractions (I–VI) Fraction II (150 g) was further chromatographed over MCI-gel CHP 20P using H_2O containing increasing amounts of MeOH to give a further five fractions. Repeated CC of fraction II-1 on Bondapak C_{18}/Porasil B and Fuji-gel ODS G3 with H_2O–MeOH (9 1) afforded compounds **1** (400 mg), **2** (90 mg), **3** (80 mg) and **4** (40 mg). Fraction II-2 was repeatedly chromatographed over Sephadex LH-20 (H_2O) and Bondapak C_{18}/Porasil B [H_2O–MeOH (9 1)] to furnish 1-*O*-galloylfructose [9].

(ii) North Korean rhubarb (950 g) was extracted and chromatographed over Sephadex LH-20 as described above to give seven fractions (I–VII) Fraction II was subsequently chromatographed over MCI-gel CHP 20P [H_2O–MeOH (0 1–1 0)] to afford a further four fractions. Repeated CC of fraction II-1 on Bondapak C_{18}/Porasil B and Fuji-gel ODS G3 furnished compounds **1** (120 mg), **3** (91 mg) and **4** (66 mg) CC of fraction II-2 over Bondapak C_{18}/Porasil B with H_2O–MeOH (9 1) yielded compound **5** (56 mg)

6-O-*Galloylsucrose* (**1**) Colourless needles (H_2O), mp 149–151°, $[\alpha]_D^{28}$ +88 6° (MeOH, *c* 0 74) FAB-MS *m/z*· 517 [M + Na]$^+$, 495 [M + H]$^+$, 153 [galloyl]$^+$, ^{1}H NMR (Me_2CO-d_6 + D_2O)· δ3.3–4.3 (11H, *m*, sugar H), 4.4–4.7 (2H, *m*, H-6′), 5.42 (1H, *d*, *J* = 4 Hz, H-1), 7 08 (2H, *s*, galloyl H) (Found: C, 42 76; H, 5 68. $C_{19}H_{26}O_{15}\cdot 2H_2O$ requires C, 43 02; H, 5 70%)

Acid hydrolysis of **1**. A soln of **1** (7 mg) in 5% aq H_2SO_4 (2 ml) was heated in a water bath for 1 hr The products were directly analysed by silica gel and cellulose TLC with C_6H_6–HCO_2Et–HCO_2H (2 7 1) (solv. 1) and *n*-BuOH–pyridine–H_2O (6:4·3) (solv 2). Gallic acid (solv. 1 R_f 0.80), glucose (solv. 2· R_f 0.44) and fructose (solv. 2 R_f 0.43) were identified by co-chromatography with authentic samples.

Enzymatic hydrolysis of **1** **1** (40 mg) and tannase (5 mg) in H_2O (10 ml) was left to stand for 2 hr with ice-cooling. The reaction mixture was concd to dryness under red. pres., and the residue treated with EtOH. The EtOH-soluble portion was subjected to CC over Sephadex LH-20. Elution with EtOH gave a hydrolysate as colourless needles (EtOH), mp 193–195°, $[\alpha]_D^{25}$ +66.5° (H_2O; *c* 0 53). This compound was identified as sucrose by direct comparison of chromatographic and physical data Further elution with EtOH yielded gallic acid (10 mg)

Partial hydrolysis of **1** A soln of **1** (70 mg) in 1% aq H_2SO_4 (6 ml) was heated in a water bath for 30 min After neutralization of the reaction mixture with $BaCO_3$, inorganic salts were filtrated off The filtrate was concd to dryness and the residue was chromatographed over Sephadex LH-20. Elution with H_2O afforded glucose. Further elution with H_2O gave **1a** as a white amorphous powder, $[\alpha]_D^{25}$ +5.6° (MeOH, *c* 0.66). FDMS *m/z*· 355 [M + Na]$^+$, 333 [M + M]$^+$, 170, ^{1}H NMR (Me_2CO-d_6 + D_2O) δ3.5–4.7 (7H, *m*, sugar H), 3.54 (8/5H, *s*, H-1), 3 66 (2/5H, *s*, H-1), and 7.15 and 7.18 (2H, each *s*, galloyl H). (Found C, 44.27, H, 5 41 $C_{13}H_{16}O_{10}\cdot H_2O$ requires C, 44.57, H, 5.18%)

Partial methanolysis of **1**. **1** (40 mg) in 0.5% H_2SO_4–MeOH (10 ml) was refluxed for 15 min The reaction mixture was neutralized with $BaCO_3$ and inorganic salts were filtrated off The filtrate was concd and subjected to CC over Sephadex LH-20 Elution with EtOH furnished methyl glucosides Further elution with EtOH afforded a mixture of hydrolysates, which were subsequently chromatographed over Bondapak C_{18}/Porasil B [H_2O–MeOH (1:0–9·1)] to give 6-*O*-galloyl methyl-β-D-fructofuranoside (**1b**) (11 mg) as a white amorphous powder, $[\alpha]_D^{25}$ −23 0° (MeOH, *c* 1 09) FD-MS *m/z* 369 [M + Na]$^+$, 347 [M + H]$^+$, 315 [M + H − MeOH]$^+$, ^{1}H NMR (Me_2CO-d_6 + D_2O) δ3.28 (3H, *s*, OMe), 3 64, 3.70 (each 1H, *d*, *J* = 12 Hz, H-1), 3 9–4 3 (3H, *m*, H-3, 4, 5), 4 27 (1H, *dd*, J = 6, 12 Hz, H-6), 4 50 (1H, *dd*, *J* = 3, 12 Hz, H-6), 7 20 (2H, *s*, galloyl H); ^{13}C NMR (Me_2CO-d_6 + D_2O) δ49.4 (OMe), 60.5 (C-1), 64 9 (C-6), 75.4 (C-4), 77 6 (C-3), 79 5 (C-5), 104 6 (C-2), 110.3 (2C) (C-2′), 120 6 (C-1′), 139.4 (C-4′), 145.7 (2C) (C-3′), 168 1 (–COO–) (Found C, 48.47, H, 5 18. $C_{14}H_{18}O_{10}$ requires C, 48.56, H, 5.24%), and methyl-α-D-fructofuranoside (**1c**) (5 mg) as a white amorphous powder, $[\alpha]_D^{25}$ +41 3° (MeOH; *c* 0 63). FDMS *m/z* 369 [M + Na]$^+$, 347 [M + H]$^+$, 315 [M + H − MeOH]$^+$, ^{1}H NMR (Me_2CO-d_6 + D_2O) δ3.34 (3H, *s*, OMe), 3 65, 3 80 (each 1H, *d*, *J* = 12 Hz, H-1), 3 9–4 3 (3H, *m*, *H*-3, 4, 5), 4 32 (1H, *dd*, *J* = 6, 12 Hz, H-6), 4 52 (1H, *dd*, *J* = 3, 12 Hz, H-6), 7 18 (2H, *s*, galloyl H) (Found C, 47.10, H, 5 15. $C_{14}H_{18}O_{10}$ 1/2H_2O requires C, 47 32, H, 5 39%).

4′-O-*Galloylsucrose* (**2**) A white amorphous powder, $[\alpha]_D^{27}$ +14 9° (MeOH, *c* 0 72). FABMS *m/z* 517 [M + Na]$^+$, 495 [M + H]$^+$, 153 [galloyl]$^+$, ^{1}H NMR (Me_2CO-d_6 + D_2O) δ3.3–4 3 (11H, *m*, sugar H), 4 56 (1H, *d*, *J* = 7 Hz, H-2′), 5.40 (1H, *t*, *J* = 7 Hz, H-3′), 5.52 (1H, *d*, *J* = 4 Hz, H-1), 7 16 (2H, *s*, galloyl H) (Found: C, 44 80; H, 5.74 $C_{19}H_{26}O_{15}$ H_2O requires C, 44 53, H, 5 50%).

Enzymatic hydrolysis of **2** An aq. soln (5 ml) of **2** (15 mg) was treated with tannase in ice-cold H_2O for 2 hr The reaction mixture was worked up as for **1** to afford sucrose (5 mg) as colourless needles (EtOH), mp 193–195°, $[\alpha]_D^{25}$ +63 8° (H_2O, *c* 0.39), and gallic acid

Partial hydrolysis of **2**. A soln of **2** (50 mg) in 0 5% H_2SO_4–MeOH (12 ml) was refluxed for 15 min The reaction mixture was treated in the same way as for **1** to furnish methyl-α- and β-glucosides and hydrolysates (**2a**) as a white amorphous powder, ^{1}H NMR (Me_2CO-d_6 + D_2O). δ3 32, 3 40 (3H in total, each *s*, OMe), 3.5–4 2 (5H, *m*, sugar H), 5 21 (3/8H, *dd*, *J* = 4, 10 Hz, H-3), 5 26 (5/8H, *t*, *J* = 7 Hz, H-3), 7 15, 7.19 (2H in total, each *s*, galloyl H).

6-O-*Galloylsucrose* (**3**) A white amorphous powder, $[\alpha]_D^{27}$ +48 0° (MeOH; *c* 0.65) FABMS *m/z*· 517 [M + Na]$^+$, 495 [M + H]$^+$, 153 [galloyl]$^+$, ^{1}H NMR (Me_2CO-d_6 + D_2O) δ3 5–4.6 (13H, *m*, sugar H), 5 46 (1H, *d*, *J* = 4 Hz, H-1), 7.16 (2H, *s*, galloyl H) (Found C, 44.52, H, 5 69. $C_{19}H_{26}O_{15}$ H_2O requires C, 44 53; H, 5 50%)

Partial hydrolysis of **3** A soln of **3** (40 mg) in 1% aq. H_2SO_4 (5 ml) was heated in a water bath for 20 min. The reaction mixture was worked up as for **1** to furnish glucose [R_f 0 43 *n*-BuOH–pyridine–H_2O (6:4.3)] and a hydrolysate This product was shown to be identical with 6-*O*-galloylglucose by direct comparison with an authentic sample [4]

1′-O-*Galloylsucrose* (**4**) A white amorphous powder, $[\alpha]_D^{27}$ + 47 0° (MeOH, *c* 0 84) FABMS *m/z* 517 $[M+Na]^+$, 495 $[M+H]^+$, 153 $[galloyl]^+$, ^1H NMR (Me_2CO-d_6+D_2O) δ3 3–4.3 (11H, *m*, sugar H), 4 31, 4 52 (each 1H, *d*, *J* = 12 Hz, H-1′), 7 16 (2H, *s*, galloyl H) (Found C, 44 10, H, 5 58 $C_{19}H_{26}O_{15}$ H_2O requires C, 44 53, H, 5 50%).

Partial hydrolysis of **4** **4** (30 mg) in 1% aq H_2SO_4 (5 ml) was heated in a water bath for 30 min Work-up as for **1** gave fructose and a hydrolysate, which was identified as 1-*O*-galloylfructose by direct comparison

2-O-*Galloysucrose* (**5**) A white amorphous powder, $[\alpha]_D^{27}$ +67 1° (MeOH, *c* 0 79) FABMS *m/z* 517 $[M+Na]^+$, 495 $[M+H]^+$, 153 $[galloyl]^+$, ^1H NMR (Me_2CO-d_6+D_2O) δ3 2–4 2 (11H, *m*, sugar H), 4 81 (1H, *dd*, *J* = 4, 10 Hz, H-2), 5 59 (1H, *d*, *J* = 4 Hz, H-1), 7 19 (2H, *s*, galloyl H) (Found C, 43 01, H, 5 74 $C_{19}H_{26}O_{15}$ $2H_2O$ requires C, 43 02, H, 5 70%)

Partial hydrolysis of **5** **5** (39 mg) was hydrolysed with 1% aq H_2SO_4 (5 ml) in the same manner as described above to yield glucose and a hydrolysate, the latter being identified as 2-*O*-galloylglucose by direct comparison with an authentic sample [Kashiwada, Y *et al*, unpublished data]

Enzymatic hydrolyses of **3–5** A soln of each sample in H_2O (5 mg/1 ml) was hydrolysed with tannase in the same manner as for **1** The solvent was evapd under red pres and the residue was subjected to TLC R_f 0 82 (gallic acid), 0 06 (sucrose) [silica gel, C_6H_6–HCO_2Et–HCO_2H (2 10.3)], R_f 0 33 (gallic acid), 0 12 (sucrose) [silica gel, $CHCl_3$–MeOH–H_2O (14 6 1)].

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