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PHENOLIC COMPOUNDS FROM *COIX LACHRYMA-JOBI* VAR. *MA-YUEN*

HIDEAKI OTSUKA, MAMI TAKEUCHI, SHOGO INOSHIRI, TOMOHIRO SATO* and KAZUO YAMASAKI†

Institute of Pharmaceutical Sciences, School of Medicine, Hiroshima University, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan; *Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu, Fukushima-ku, Osaka 553, Japan

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Key Word Index—*Coix lachryma-jobi* var. *ma-yuen*; Gramineae; adenosine; lignan; 4-ketopinoresinol; 1-*C*-syringylglycerol; 2,6-dimethoxy-*p*-hydroquinone 1-*O*-glucoside; X-ray analysis; ^{13}C NMR.

Abstract—Four phenolic compounds and adenosine were isolated from the roots of *Coix lachryma-jobi* var. *ma-yuen*. On the basis of spectral evidence and the results of chemical synthesis, the structures of three were determined to be 4-ketopinoresinol, and *threo*- and *erythro*-1-*C*-syringylglycerol. The aglycone moiety of a new glucoside, 2,6-dimethoxy-*p*-hydroquinone 1-*O*-*β*-D-glucopyranoside, was determined from ^{13}C and ^{1}H NMR spectra and the position of the *O*-glucosyl moiety was confirmed by single-crystal X-ray analysis.

INTRODUCTION

In a previous paper [1], we reported the isolation of coixol, benzoxazinone and four benzoxazinone glucosides from the roots of *Coix lachryma-jobi* L. var. *ma-yuen* Stapf (Gramineae), and the aglycones of these compounds were found to inhibit histamine release from rat mast cells induced by concanavalin A and by immunoglobulin E[2]. On further investigation of the roots of this plant, six compounds (**1**–**6**) were isolated from the butanol-soluble fraction of a chloroform–methanol extract. We now describe the isolation and structure elucidation of these compounds, adenosine (**1**), 4-keto-2,6-bis(3-methoxy-4-hydroxyphenyl)3,7-dioxabicyclo[3,3,0]octane (4-ketopinoresinol) (**2**), *threo*- and *erythro*-1-*C*-syringylglycerol (**4** and **5**), and 2,6-dimethoxy-*p*-hydroquinone 1-*O*-*β*-D-glucopyranoside (**6**).

RESULTS AND DISCUSSION

Compound **1** was identified as adenosine, by direct comparison with an authentic sample. Compound **2**, $C_{20}H_{20}O_7$, showed ^{13}C NMR signals for two sets of 1,2,4-trisubstituted benzene rings, two Ph–CHO–(*d*, *δ* 84.7 and 83.4), two –CH–, one $-CH_2-$, a carbonyl carbon (*δ* 177.0) and two methoxyl carbons (Table 1). In the IR spectrum, the carbonyl absorption at 1760 cm^{-1} suggested that compound **2** had a *γ*-lactone system. From these and the ^{1}H NMR data, **2** was determined to be the lignan: 4-keto-2,6-bis(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3,3,0]octane(4-keto-pinoresinol). This compound has been isolated from *Aegilops ovata* as a germination inhibitor, but ^{13}C NMR data were not reported[3–5]. Although there is some ambiguity as to the determination of aryl positions, i.e. 2,6-diaryl or 2,4-diaryl(6,8-diaryl in this case), since the ^{1}H and ^{13}C NMR chemical shifts and coupling constants of the dioxabicyclooctane ring matched the reported data for 4-ketosesamine (**3**), **2** must have the same aryl group arrangement as 4-ketosesamine[4, 6–8] (Table 1).

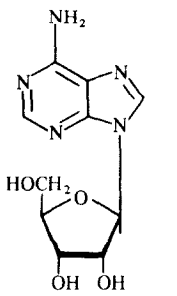
Compounds **4** and **5** showed similar behaviour on TLC(R_f: 0.40; silica gel, $CHCl_3$–MeOH–H_2O = 15 : 6 : 1) and were finally purified by preparative HPLC (**5** eluted faster). These compounds showed similar ^{1}H and ^{13}C NMR spectra (Table 2). ^{13}C NMR suggested that

Table 1. ^{13}C NMR data for compounds **2** and **3** (25 MHz, $CDCl_3$, TMS as int. standard)

C	**2**	**3**†
1	53.4 *d*	53.2
2	83.4 *d**	83.3
4	177.0 *s*	176.4
5	50.0 *d*	49.9
6	84.7 *d**	84.3
8	72.7 *t*	72.6
1′, 1″	131.1 *s*	132.9
	132.3 *s*	134.2
2′, 2″	107.9 *d*	105.6*
	108.2 *d*	105.8*
3′, 3″	145.4 *s*	147.1
4′, 4″	146.1 *s*	147.8
	146.8 *s*	148.2
	147.0 *s*	
5′, 5″	114.4 *d*	108.2*
	114.8 *d*	108.4*
6′, 6″	118.1 *d*	118.6
	118.4 *d*	118.9
–OMe	56.0 *q* × 2	—
OCH_2O	—	101.1
		101.3

*Assignments may be interchanged in the same column.
†Data taken from ref. [7].

†Author to whom correspondence should be addressed.



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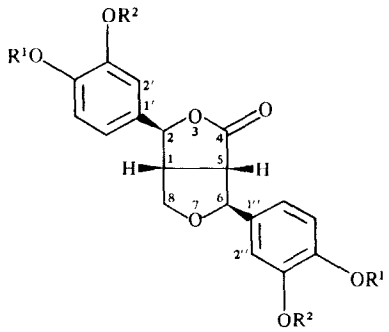
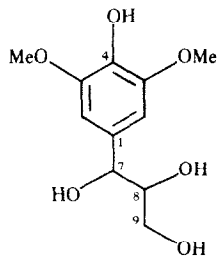
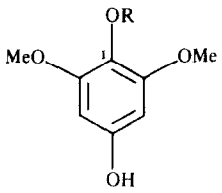


2 R^1 = H, R^2 = Me
3 R^1, R^2 = —CH_2—



4 *threo*-
5 *erythro*-



6 R = Glc
7 R = H

both compounds have syringyl and α-substituted glycerol moieties, and these were geometric isomers. Due to the low amount of the samples (*ca* 2 mg each), their structures were confirmed by the synthesis of *threo*-1-*C*-syringylglycerol from the corresponding cinnamic acid derivative through the *cis*-addition of two hydroxyl groups to a *trans* double bond[9]. The ^{13}C and ^1H NMR spectra of this synthetic isomer were superimposable on those of **4**, and it also showed the same retention time (5.40 min) on HPLC (TSK gel ODS-120A, MeCN–MeOH–H_2O = 1 : 1 : 98) [cf: *erythro*-1-*C*-syringylglycerol (**5**): R_t; 3.50 min].

Table 2. ^{13}C NMR data for compounds **4**–**7** (25 MHz, DMSO-d_6, TMS as int. standard)

C	4	5	C	6	7
1	134.1 *s**	134.1 *s**	4	153.8 *s*	149.8 *s*†
2	104.1 *d*	104.5 *d*	3	93.7 *d*	93.3 *d*
3	147.4 *s*	147.3 *s*	2	153.0 *s*	148.5 *s*†
4	133.4 *s**	133.4 *s**	1	127.4 *s*	127.9 *s*
5	147.4 *s*	147.3 *s*	6	153.0 *s*	148.5 *s*†
6	104.1 *d*	104.5 *d*	5	93.7 *d*	93.3 *d*
7	72.9 *d*	74.1 *d*			
8	75.8 *d*	75.3 *d*			
9	62.5 *t*	62.9 *t*			
–OMe	55.8 *q* × 2	55.8 *q* × 2		56.0 *q* × 2	55.6 *q* × 2
			1′	103.4 *d*	—
			2′	74.1 *d*	—
			3′	76.9 *d**	—
			4′	69.9 *d*	—
			5′	76.3 *d**	
			6′	60.9 *d*	—

*Assignments may be interchanged in the same column.

†Assignments were made in the non-NOE mode with a long repetition time (20 sec).

These compounds have been reported to be degradation products arising on the hydrolysis of lignins in water or acidic media [10–14], and to be synthetic materials [15]. Two analogous compounds, namely 3,4,5-trimethoxyphenyl-1-*C*-glycerol and 4-hydroxyphenyl-1-*C*-glycerol, were reported to be a metabolite of 3,4,5-trimethoxyallylbenzene in rats [16] and to be enzymically formed from 4-hydroxycinnamyl alcohol [17], respectively. As there has been no report of syringylglycerols having been isolated as natural products, it is possible that **4** and **5** were derived from lignins during the extraction and purification procedures.

Compound **6**, colourless needles, $C_{14}H_{20}O_9$, was obtained by preparative HPLC. ^{13}C NMR showed four signals in the aromatic region (δ 93.7, 127.4, 150.3 and 150.8) and one methoxyl signal, and six carbons for the β-glucopyranosyl moiety (Table 2). This suggested that the aromatic portion was symmetrically substituted. As it is a monoglucoside, only one structure is possible, namely 2,6-dimethoxy-*p*-hydroquinone. The 1-position carries the glucosyl moiety as the ^{13}C NMR substitution-induced shift trend indicates this. The β-glucosylation shift values for arbutin [$\Delta\delta = \delta$ (arbutin)-δ (hydroquinone)] as to the *ipso*, *ortho*, *meta* and *para* carbons were +0.5, +1.9, −0.3 and +2.3, respectively (in DMSO-d_6) [18]. These Δδ values were used to calculate the expected chemical shifts of the possible glucosides of 2,6-dimethoxy-*p*-hydroquinone. On going from the 2,6-dimethoxy-*p*-hydroquinone, **7** [δ C(1–6) = 127.9, 148.5, 93.3, 149.8, 93.3 and 148.5, in DMSO-d_6, respectively], the calculated chemical shifts of all carbons, as a 1-glucosyl derivative, were within 2.6 ppm, whereas for a 4-glucosyl derivative, the maximum difference of calculated chemical shifts from observed values was 4.8 ppm. To confirm this, X-ray analysis was performed. A computer-generated perspective drawing of the final X-ray model for **6** with the hydrogens is shown in Fig. 1. Although the X-ray study defined only the relative configuration, as the sign of

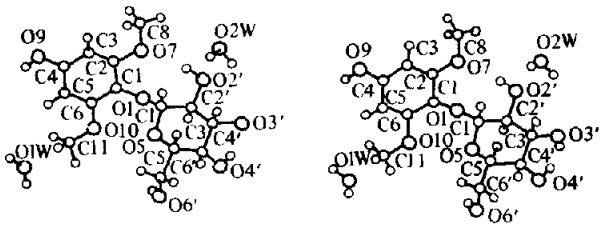


Fig. 1.

optical rotation of **6** is the same as that of methyl β-D-glucopyranoside, the glucose of **6** must be in the D series. For determination of the glucosyl positions of tachioside and isotachioside, calculated β-glucosylation shift values were matched with the observed values [18]. Also in this case, that analogy can be extended, since calculated chemical shifts as 1-glucosyl derivative were matched more with the observed values.

Although the structurally related tachioside (methoxy-*p*-hydroquinone-4-β-D-glucopyranoside) [18], isotachioside (methoxy-*p*-hydroquinone-1-β-D-glucopyranoside) [18, 19] and 2,4,6-trimethoxyphenol-1-*O*-β-D-(6′-*O*-galloyl)-glucopyranoside [20] have been reported, to our knowledge, **6** has not been previously reported to occur in Nature.

In the course of a search for natural compounds which inhibit histamine release from rat mast cells, we found that dimethoxy-*p*-hydroquinone from *Berchemia racemosa* showed strong activity; $IC_{50} = 8\ \mu M$ [21], with concanavalin A. Dimethoxy-*p*-hydroquinone itself is widely distributed in plants as a degradation product from some lignans [21].

It is interesting that benzoxazinones from this plant generally inhibit histamine release, but their glucosides are almost completely inactive [2]. We expected the same to be the case for **6**. When it is administered to some living systems, glucose is liberated by some endogenous glucosidase, and the 2,6-dimethoxy-*p*-hydroquinone thus formed is automatically and/or enzymatically oxidized to a quinone system that shows some activity.

EXPERIMENTAL

Mp: uncorr, ^{1}H NMR and ^{13}C NMR: 100 and 25 MHz, respectively; MS; 75 eV.

Plant material. C. lachryma-jobi L. var. *ma-yuen* Stapf was cultivated at Yasufuruichi (Hiroshima City) and harvested in November, 1982.

Extraction and separation of compounds. The dried and powdered roots (3.5 kg) of the plant were extracted with hexane, Me_2CO and a mixture of MeOH–$CHCl_3$ (2:1), successively. The MeOH–$CHCl_3$ extract was suspended in H_2O and then extracted with *n*-butanol to give an extract (40 g) which was chromatographed on a highly porous polymer(Diaion, HP 20; Mitsubishi Chemical Ind. Co.) with a stepwise increase of MeOH content in H_2O (10, 20, 30, . . . , 100%). The 10–30% MeOH eluent from the Diaion column was subjected to CC (silica gel, $CHCl_3$–MeOH), low pressure LC (Lichroprep RP-8: MeOH–H_2O) and prep. TLC (silica gel, $CHCl_3$–MeOH–H_2O = 15:6:1) to give **1** (31 mg). From another silica gel CC fraction, **3** (10.5 mg) was obtained by Sephadex LH-20 CC(MeOH) and prep. HPLC (TSK gel ODS 120 T, 5% MeOH), and further purification of the fraction recovered on the former prep. HPLC by prep. HPLC (TSK gel ODS 120T, MeCN–MeOH–H_2O = 1:1:98) gave **4** (2.05 mg) and **5** (1.55 mg). From the 80–90% MeOH eluent from the Diaion column, **2** (10.7 mg) was purified by silica gel CC($CHCl_3$–MeOH), Sephadex LH-20 CC(MeOH) and prep. HPLC(TSK gel silica-60, hexane–EtOH–H_2O = 425:75:2).

Adenosine (**1**). ^{1}H NMR(DMSO-d_6): δ 4.00 (1H, *dd*, *J* = 3, 6 Hz, H-4′), 4.19 (1H, *dd*, *J* = 3, 5 Hz, H-3′), 4.63 (1H, *t*, *J* = 6 Hz, H-2′), 5.91 (1H, *d*, *J* = 6 Hz, H-1′), 7.39 (2H, *s*, $-NH_2$), 8.17 (1H, *s*, H-2), 8.39 (1H, *s*, H-8); ^{13}C NMR (DMSO-d_6): δ 61.5 (*t*, C-5′), 70.5 (*d*, C-3′), 73.4 (*d*, C-2′), 85.8 (*d*, C-4′), 87.8 (*d*, C-1′), 119.1 (*s*, C-5), 139.9 (*d*, C-8), 148.9 (*s*, C-4), 152.3 (*d*, C-2), 156.0 (*s*, C-6).

4-Keto-2,6-bis(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo-[3,3,0]octane(4-ketopinoresinol) (**2**). Amorphous powder, $[\alpha]_D^{20}$ +54.7° (MeOH; *c* 0.71). HR-EIMS *m/z*: 372.1221 $[M]^+$ (calc. 372.1208, $C_{20}H_{20}O_7$); EIMS *m/z* (rel. int.): 372 $[M]^+$ (47), 191 (13), 163 (31), 151 (100), 137 (40), 123 (60); IR ν_{max}^{KBr} cm^{-1}: 3400, 2900, 1760, 1605, 1515, 1026; UV λ_{max}^{MeOH} nm: 232, 280, 285 sh; ^{1}H NMR ($CDCl_3$): δ 3.25 (1H, *m*, H-1), 3.48 (1H, *dd*, *J* = 3.9 Hz, H-5), 3.89 (6H, *s*), 4.03 (1H, *dd*, *J* = 4.9 Hz, H-8), 4.34 (1H, *dd*, *J* = 6, 9 Hz, H-8′), 5.33 (1H, *d*, *J* = 3 Hz, H-2), 5.35 (1H, *d*, *J* = 3 Hz, H-6), 5.73 (2H, *br s* × 2, –OH), 6.73–6.97 (6H, *m*, aromatic H); ^{13}C NMR ($CDCl_3$): see Table 1.

threo-1-C-*Syringylglycerol* (**4**). UV λ_{max}^{MeOH} nm: 230 sh, 270, 278 sh; ^{1}H NMR (DMSO-d_6): δ 3.73 (6H, *s*), 4.3 (3H, *m*), 4.95 (1H, *d*, *J* = 5 Hz, H-7), 6.58 (2H, *s*, aromatic H), 8.14 (1H, *s*, phenolic –OH); ^{13}C NMR: see Table 2.

erythro-1-C-*Syringylglycerol* (**5**). UV λ_{max}^{MeOH} nm: 225 sh, 275; ^{1}H NMR (DMSO-d_6): δ 3.74 (6H, *s*), 4.3 (3H, *m*), 5.10 (1H, *d*, *J* = 5 Hz, H-7), 6.59 (2H, *s*, aromatic H), 8.11 (1H, *s* phenolic –OH); ^{13}C NMR: see Table 2.

2,6-*Dimethoxy*-p-*hydroquinone* 1-*O*-β-D-*glucopyranoside* (**6**). Colourless needles from (Me_2CO–H_2O, mp 232–234°, $[\alpha]_D^{20}$ −20.5° (MeOH, *c* 0.68); HR−FABMS *m/z* 355.1020, requires $[M+Na]^+$ 355.1004 for $C_{14}H_{20}O_9Na$; IR ν_{max}^{KBr} cm^{-1} 3300, 1603, 1505, 1480, 1215, 1130, 1065, 955, 810; UV λ_{max}^{MeOH} nm: 278; ^{1}H NMR (DMSO-d_6): δ 3.69 (6H, *s*), 4.65 (1H, *d*, *J* = 6 Hz, anomeric H), 6.07 (2H, *s*, aromatic H), 9.26 (1H, *s*, phenolic –OH); ^{13}C NMR: see Table 2.

HPLC analysis of **4** and **5**. HPLC analysis was performed on a TSK-gel ODS-120A (10 μm) column (4 × 150 mm; MeCN–MeOH–H_2O 1:1:98, at 25°, 1.5 ml/min; detection: UV at 254 nm). The R_t (min) of compounds **4** and **5** were 5.40 and 3.50, respectively. Synthetic *threo*-1-*C*-syringylglycerol was eluted at the same R_t as compound **4** (5.40 min).

Synthesis of threo-1-*C*-*syringylglycerol* **4**. 3,5-Dimethoxy-4-*O*-acetylcinnamic acid ethyl ester (1 g) was oxidized with 358 mg $KMnO_4$ and 135 mg $MgSO_4$ in 50% Me_2CO at 0° for 6 hr [9]. The product was taken up in Et_2O and then purified by silica gel CC (C_6H_6–Me_2CO = 9:1) to give 443 mg colourless crystals, from hexane–$CHCl_3$. mp 100–102°. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, *t*, *J* = 7 Hz), 2.13 (3H, *s*), 3.67 (2H, *m*), 3.76 (6H, *s*), 4.19 (2H, *q*, *J* = 7 Hz), 6.64 (2H, *s*); ^{13}C NMR($CDCl_3$): δ 14.0, 20.4, 56.1, 62.0, 74.6, 75.0, 103.1, 128.1, 138.8, 152.0, 169.0, 172.0. After acetylation of the diol–monoacetate–ethylester (400 mg), the triacetate was reduced with $LiAlH_4$ (100 mg) in 80 ml Et_2O under reflux for 4 hr. After the addition of 10% H_2SO_4 and evapn of the organic solvent, the product was taken up in *n*-BuOH and then washed with NaCl satd H_2O and 5% $NaHCO_3$. Sephadex LH-20 CC(MeOH) and recrystallization from $CHCl_3$–MeOH gave 95 mg colourless crystals. Mp 103–104°, lit [11] mp 113°. IR ν_{max}^{KBr} cm^{-1}: 3250, 1610, 1515, 1455, 1420, 1215, 1110; UV λ_{max}^{MeOH} nm (log ε): 230 sh (3.85), 271 (3.13), 280 sh (2.99); EIMS *m/z* (rel. int.): 244 $[M]^+$ (20), 181 (90), 180 (100), 179 (64), 165(32), 123 (37), 76 (26). ^{1}H NMR (DMSO-d_6): δ 3.74 (6H, *s*), 4.4 (3H, *m*), 4.93 (1H, *d*, *J* = 5 Hz, H-7), 6.59 (2H, *s*, aromatic H), 8.10 (1H, *s*, phenolic –OH); ^{13}C NMR (DMSO-d_6): δ 55.8, 62.6, 73.0, 75.8, 104.1, 133.4, 134.2, 147.4.

Synthesis of 2,6-*dimethoxy*-p-*hydroquinone* (**7**). 1,3,5-Trimethoxybenzene (10 g) was treated with a mixture of 100 ml of EtOH and 100 ml of 30% HNO_3 at 55° for 2.5 hr [22]. The 2,6-dimethoxy-*p*-benzoquinone thus formed was extracted with $CHCl_3$, and then the organic layer washed with H_2O, 5% $NaHCO_3$ and H_2O successively. After evapn of the solvent, the residue was recrystallized from HOAc to give 5.14 g yellow needles. mp 250–253°, sublimes from *ca* 180°, lit [22] mp 249°. IR ν_{max}^{KBr} cm^{-1}: 1695, 1640, 1593; UV λ_{max}^{MeOH} nm (log ε): 285 (4.08), 375 (2.48). EIMS *m/z* (rel. int.): 168 $[M]^+$ (18), 153 (1), 140 (2), 138 (6), 125 (4), 112 (2), 95 (5), 80 (11), 69 (100), 53 (14), 41 (11), 15 (85). ^1H NMR ($CDCl_3$) δ 3.83 (6H, *s*), 5.86 (2H, *s*); ^{13}C NMR ($CDCl_3$) δ 56.3, 107.1, 156.8, 176.0, 186.2. One g 2,6-dimethoxy-*p*-benzoquinone was reduced with 50 ml of satd $Na_2S_2O_4$ and 100 ml EtOH at room temp. for 2 hr [23]. The product was taken up in Et_2O and recrystallization from C_6H_6–MeOH afforded colourless needles (485 mg). Mp 159–161°, lit [24] mp 158°, IR ν_{max}^{KBr} cm^{-1}: 3250, 1640, 1525; UV λ_{max}^{MeOH} nm (log ε): 283 (3.57); EIMS *m/z* (rel. int.): 170 $[M]^+$ (100), 155 (52), 127 (33); ^1H NMR (DMSO-d_6): δ 3.69 (6H, *s*), 6.05 (2H, *s*), 7.47 (1H, *s*, –OH), 8.79 (1H, *s*, –OH); ^{13}C NMR: see Table 2.

Single-crystal X-ray diffraction study on **6**. Suitable crystals of **6**, in the form of needles, could be grown on slow evapn of Me_2CO–H_2O solns. A crystal of the dimensions, $0.10 \times 0.15 \times 0.30$ mm, was used for all X-ray measurements on a Rigaku AFC-5 diffractometer with graphite-monochromated CuKα radiation. Lattice parameters were determined from 24 reflections ($45° < 2\theta < 55°$). Integrated intensities were measured in the range of $2\theta \leqq 130°$ with an $\omega/2\theta$ scan: $0 \leqq h \leqq 13$, $0 \leqq k \leqq 8$, $-12 \leqq l \leqq 12$. Of 1567 independent reflections measured, 1527 with $I \geqq 2(\sigma)$ were considered to have been observed. No absorption correction was performed. Structure was solved by direct methods. H atoms were located from a difference Fourier map, and their positions were refined with isotropic thermal parameters. The structure was refined by full matrix least-squares with anisotropic thermal parameters for non-H atoms. The isotropic type-I extinction correction was applied [25]. $\Sigma w(\Delta F)^2$ was minimized with $w = 1$. Finally $R = 0.030$, $WR = 0.031$ and the extinction parameter was $g = 0.20(1) \times 10^{-4}$, $|\text{shift}/\sigma|_{max} < 0.1$ and $-0.19 \leqq \Delta\rho \leqq 0.16\ eA^{-3}$. All crystallographic calculations were made with a VAX11/780 computer using the programme system, XTAL2.2 [26], with the scattering factors included in the programme. Crystal data; $C_{14}H_{20}O_9 \cdot 2H_2O$, $M_r = 368.3$, monoclinic, space group $P2_1$, $a = 11.618(1)$ Å, $b = 6.950(1)$Å, $c = 10.552(1)$Å, $\beta = 98.45(1)°$, $V = 842.7(1)$ Å^3, $Z = 2$, $D_x = 1.452$ g/cm^3, $D_m = 1.46$ g/cm^3, CuKα radiation, $\lambda = 1.54178$ Å, $\mu = 1.11$ mm^{-1}, $F(000) = 392$, room temp. The atomic coordinates of this structure have been deposited at the Cambridge Crystallographic Data Centre.

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