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ScienceDirect
Phytochemistry 69 (2008) 1215–1219
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

7-*O*-Methylated anthocyanidin glycosides from *Catharanthus roseus*

Kenjiro Toki [a], Norio Saito [b], Yuki Irie [a], Fumi Tatsuzawa [c,*], Atsushi Shigihara [b], Toshio Honda [b]

[a] *Laboratory of Floriculture, Faculty of Horticulture, Minami-Kyushu University, Takanabe, Miyazaki 884-0003, Japan*
[b] *Faculty of Pharmaceutical Sciences, Hoshi University, Shinagawa, Tokyo, 142-8501, Japan*
[c] *Experimental Farm, Faculty of Horticulture, Minami-Kyushu University, Takanabe, Miyazaki 884-0003, Japan*

Received 28 August 2007; received in revised form 27 September 2007
Available online 27 December 2007

Abstract

Anthocyanins were isolated from orange–red flowers of *Catharanthus roseus* cv 'Equator Deep Apricot', and identified as rosinidin 3-*O*-[6-*O*-(α-rhamnopyranosyl)-β-galactopyranoside] (**1**), and also 7-*O*-methylcyanidin 3-*O*-[6-*O*-(α-rhamnopyranosyl)-β-galactopyranoside] (**2**) by chemical and spectroscopic methods. Pigment **1** was found to be a major anthocyanin in the flowers of this cultivar. By contrast, the distribution of rosinidin glycosides is very limited in plants, and reported only in the flowers of *Primula*. Pigment **2** was found in smaller concentrations, but its aglycone, 7-*O*-methylcyanidin, has been reported only once before, from the fruit of mango.

Keywords: *Catharanthus roseus*; Apocynaceae; 7-*O*-Methylcyanidin 3-robinobioside; Rosinidin 3-robinobioside; Orange–red flower color

1. Introduction

Catharanthus roseus (Apocynaceae) is native to Madagascar with either orange–red, red, purple red, red purple or white flowers. *C. roseus* is not only a well known ornamental plant, but it is also a very important medicinal species. It produces vinblastine, which in the last 20 years have saved the lives of thousands of cancer patients, especially those with various forms of lymphoma. Isolation of anthocyanins from the flowers and callus of *C. roseus* was already studied by Forsyth and Simmonds (1957) and Carew and Krueger (1976), and they reported the presence of an unusual methylated anthocyanidin, hirsutidin, only known otherwise in *Primula* and *Dionysia* in the Primulaceae (Karrer and Widmer, 1927; Harborne, 1958, 1960, 1963, 1968) and *Prunella* in the Labiatae (Harborne and Baxter, 1999). Also, six glycosides, 3-glucosides and 3-*p*-coumaroylglucosides of hirsutidin, malvidin and petunidin, were isolated from *in vivo* and *in vitro* plants of *C. roseus* (Piovan et al., 1998; Filippini et al., 2003).

In a survey of anthocyanins in the flowers of *C. roseus* by TLC and HPLC, we found two novel anthocyanins in the aqueous acetic acid extract from the orange–red flowers, whose anthocyanidins were characteristically methylated at the 7-OH group such as rosinidin and 7-*O*-methylcyanidin, respectively. In this paper, we wish to report the structure elucidation of two novel 7-*O*-methylanthocyanidin glycosides isolated from the deep orange–red flowers of *C. roseus* 'Equator Deep Apricot'.

2. Results and discussion

2.1. Anthocyanins in the extract from the orange–red flowers

Two major and three minor anthocyanin peaks were observed in the 5% acetic acid extract from the deep orange–red flowers of *C. roseus* 'Equator Deep Apricot' using HPLC monitored at 520 nm. The proportions were 48.2% (pigment **1**), 25.3% (pigment **2**), 10.9% (pigment **3**), 7.9% (pigment **4**), and 2.7% (pigment **5**) based on the percentage of the total absorbance of the anthocyanin peaks. The two anthocyanins, pigments **1** and **2**, were then

* Corresponding author. Tel./fax: +81 983 22 6835.
E-mail address: fumi@nankyudai.ac.jp (F. Tatsuzawa).

0031-9422/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2007.11.005

extracted from the dried flowers with 5% aqueous acetic acid, and purified using column chromatography (CC) (Diaion HP-20 and Sephadex LH20), preparative PC and HPLC, according to the procedures described previously (Toki et al., 2001). However, the other minor pigments **3**–**5** could not be obtained in pure form due to their small amounts. The chromatographic and spectroscopic properties of pigments **1** and **2** are summarized in Table 1.

Acid hydrolysis of both pigments **1** and **2** gave unknown anthocyanidins **A** and **B,** respectively**,** as aglycones together with galactose and rhamnose as their sugar components. The structures of both unknown anthocyanidins were presumed to be rosinidin (**A**) for pigment **1** and 7-*O*-methylcyanidin (**B**) for pigment **2** by the results of TLC, HPLC and spectroscopic properties (Table 1 and Berardini et al., 2005; Harborne, 1967, 1968, 1984). The structures of both anthocyanidins were confirmed by the analyses of their FAB MS (HRMS) and NMR spectra (500 MHz in CF_3CO_2D–CD_3OD, 1:9) (Table 1, Sections 4.4.1 and 4.4.2).

Moreover, the structures of both pigments **1** and **2** were elucidated on the basis of the analysis on their ^1H and ^{13}C NMR spectra [500 MHz for ^1H and 125.78 MHz for ^{13}C spectra in CF_3CO_2D–DMSO-d_6 (1:9) or CF_3CO_2D–CD_3OD (1:9)], including 2D COSY, 2D NOESY, HMQC, HMBC and negative difference NOE (DIFNOE) spectra.

2.2. Pigment 1

The molecular ion $[M]^+$ of pigment **1** was observed at *m/z* 623 ($C_{29}H_{35}O_{15}$), indicating that pigment **1** is composed of 7,3′-*O*-dimethylcyanidin (rosinidin) with one molecule each of rhamnose and a hexose, which was identified as galactose after acid hydrolysis. The elemental components were confirmed by measuring its HRMS (Section 4.4.3).

The structure of pigment **1** was elucidated based on analysis of its ^1H NMR spectra. The chemical shifts of six aromatic protons of the anthocyanidin moiety were assigned as shown in Table 2. These values are identical with those of anthocyanidin **A** obtained by acid hydrolysis of pigment **1**. Six proton signals corresponding to two methyl groups of 7,3′-*O*-dimethylcyanidin were observed at δ 4.04 (*s*, 3H at 7-*O*-methyl group) and δ 3.99 (*s*, 3H at 3′-*O*-methyl group). By measurement of its NOESY spectrum, strong long range NOEs between a signal of H-8 (δ 7.42, *br s*) of the aglycone moiety and three proton resonances (δ 4.04, *s*) of the 7-*O*-methylgroup, and also H-2′ (δ 8.26, *d*, $J = 1.9$ Hz) of the aglycone moiety and three proton signals (δ 3.99, *s*) of the 3′-*O*-methyl group were observed (Fig. 1). These results indicated that both the OH-7 and OH-3′ groups of anthocyanidin of pigment **1** were methylated. Therefore, the structure of this aglycone of pigment **1** was unambiguously confirmed to be 7,3′-*O*-dimethylcyanidin, rosinidin, as indicated in Section 2.1. The chemical shifts of the sugar moieties were observed in the region of δ 5.41–1.15, where the two anomeric protons

Table 2
NMR spectroscopic data of anthocyanins from *Catharanthus roseus*

	Pigment 2		Pigment 1	
	^{13}C δ(ppm)[a]	^1H δ(ppm)[b]	^{13}C δ(ppm)[a]	^1H δ(ppm)[b]
Anthocyanindin				
2	163.2		163.1	
3	145.0		145.3	
4	133.0	8.96 *s*	134.5	8.92 *s*
5	155.9		156.8	
6	102.4	6.70 *s*	102.2	6.78 *d* (1.9)
7	168.1		168.5	
8	92.2	7.17 *s*	92.5	7.42 *d* (1.9)
9	156.7		155.7	
10	112.5		112.7	
1′	119.9		119.6	
2′	118.1	8.14 *d* (2.5)	114.7	8.26 *d* (1.9)
3′	146.4		148.4	
4′	155.2		156.1	
5′	116.8	7.04 *d* (8.9)	116.9	7.15 *d* (8.9)
6′	127.7	8.33 *dd* (2.5, 8.9)	128.6	8.39 *dd* (1.9, 8.9)
7-*O*-CH_3	55.2	4.04 *s*	57.2	4.04 *s*
3′-*O*-CH_3	–		56.2	3.99 *s*
Galactose				
1	102.4	5.29 *d* (8.0)	102.8	5.41 *d* (7.6)
2	70.2	4.01 *dd* (8.0, 9.8)	75.1	3.86 *dd* (7.6, 9.2)
3	69.4	3.68 *dd* (3.1,9.8)	68.6	3.80 *m*
4	68.7	3.92 *br d* (3.1)	70.5	3.67 *br s*
5	74.6	4.02 *m*	74.6	4.03 *m*
6a	61.2	3.79 *m*	66.1	3.78 *m*
6b		3.87 *dd* (4.3, 11.0)		3.53 *dd* (7.8, 10.7)
Rhamnosc				
1	98.7	4.62 *d* (1.3)	100.6	4.54 *br s*
2	70.5	3.76 *dd* (1.3, 3.4)	70.3	3.61 *br s*
3	71.0	3.64 *m*	70.9	3.47 *dd* (3.4, 9.5)
4	72.3	3.34 *m*	72.2	3.19 *t* (9.2)
5	65.2	3.61 *m*	68.6	3.40 *dd* (6.4, 9.5)
CH_3	18.2	1.23 *d* (6.2)	18.1	1.15 *d* (6.4)

[a] DMSO-d_6/CF_3CO_2D = 9:1.

Table 1
Chromatographic and spectroscopic properties of anthocyanins from *Catharanlhus roseus*

Anthocyanins[a]	Rf value (×l00)						Rt (min)	Spectral data in 0.1% HCl–MeOH				FAB-MS
	Forestal	Formic	BAW	BuHCl	1%HC1	HOAc–HCl		λ_{max} (nm)	E_{acyl}/E_{max}	E_{440}/E_{max}	A1C1$_3$	$[M]^+$
Pigment 1			73	23	26	66	23.7	282, 524	12	21	–	623
Pigment 2			58	18	20	58	19.5	282, 525	11	19	+	609
Aglycone of **Pigment 1**	88	60					37.6	276, 530	–	20	–	315
Aglycone of **Pigment 2**	71	43					28.6	276, 532	–	18	+	301
Cyanidin	56	33					22.6	275, 538	–	19	+	
Peonidin	73	48					29.1	274, 537	–	38	–	

[a] Pigment 1; Rosinidin 3-rhamnosylgalactoside, Pigment 2; 7-*O* -Methylcyanidin 3-rhamnosylgalactoside.

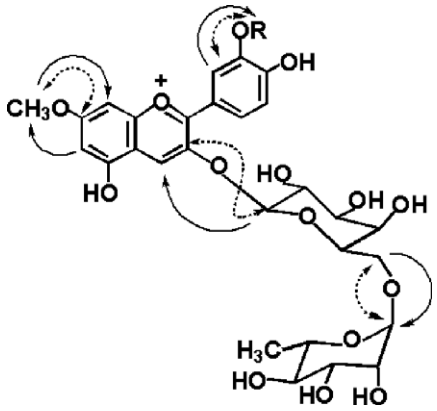

Fig. 1. 7-*O*-methylcyanidin 3-*O*-[6-*O*-(α-L-rhamnopyranosyl)-β-D-galactopyranoside] (R=H), and rosinidin 3-robinobioside (R=CH_3). Observed NOE's are indicated by arrows. Observed HMBC correlations are indicated by dotted arrows.

resonated at δ 5.41 (*d*, *J* = 7.6 Hz, Gal-H-1) and δ 4.54 (*s*, Rhamnose H-1). Based on the observed coupling constants (Table 2), galactose was assumed to be in the β-pyranose form and rhamnose to be in the α-pyranose form.

In the NOESY spectrum, the correlations between H-4 (δ 8.92) of the anthocyanidin moiety and H-1 (δ 5.41, *d*, *J* = 7.6 Hz) of Gal, and also H-1 (δ 4.54, *s*) of rhamnose and H-6b (δ 3.53, *dd*, *J* = 7.8, 10.7 Hz) of Gal were observed, respectively suggesting that the OH-3 of anthocyanidin moiety was glycosylated with galactose and also the OH-6 of galactose was bonded to the OH-1 of rhamnose. These results were also confirmed by the analysis of its ^{13}C NMR and HMBC spectrum (Fig. 1).

Consequently, the structure of pigment **1** was determined to be 7,3′-*O*-dimethylcyanidin 3-*O*-[6-*O*-(α-rhamnopyranosyl)-β-galactopyranoside], which is a new anthocyanin in plants (Harborne and Baxter, 1999; Williams and Grayer, 2004; Andersen and Jordheim, 2006).

2.3. Pigment 2

The molecular ion $[M]^+$ of pigment **2** was observed at *m*/*z* 609 (calc. for $C_{28}H_{33}O_{15}$, 609.181) using FABMS, indicating that pigment **2** is composed of 7-*O*-methylcyanidin with one molecule each of a rhamnose and a hexose, which was identified as galactose after acid hydrolysis. The elemental components were confirmed by measuring its HRMS (Section 4.4.4).

The structure of pigment **2** was further elucidated on the basis of analysis on its NMR spectra in the same process described in Section 2.2.

The chemical shifts of six aromatic protons of its anthocyanidin moiety were assigned as shown in Table 2, and these values were in agreement with those of aglycone, 7-*O*-methylcyanidin (Section 2.1. and Table 2). The ^1H NMR spectrum exhibited three proton signals at δ 4.04 (*s*) corresponding to a methyl group at the OH-7 of anthocyanidin moiety. By analysis of its NOESY spectrum, long range NOEs between H-8 (δ 7.17) of anthocyanidin and three proton signals (δ 4.04, *s*) of the methyl group were observed (Fig. 1) suggesting that the OH-7 group of the anthocyanidin moiety was methylated. Thus, the structure of this anthocyanidin moiety is unambiguously determined to be 7-*O*-methylcyanidin.

The chemical shifts of the sugar moieties were observed in the region of δ 5.29–1.23, where two anomeric protons were assigned at δ 5.29 (*d*, *J* = 8.0 Hz, Gal-H-1) and δ 4.62 (*d*, *J* = 1.3 Hz, Rha H-1). Based on the observed coupling constants of the sugar moieties (Table 2), galactose was assumed to be in the β-pyranose form and rhamnose to be in the α-pyranose form.

In the NOESY spectrum, the correlations between H-4 (δ 8.96) of the anthocyanidin moiety and H-1 (δ 5.29) of Gal, and H-1 (δ 4.62) of Rha and H-6a, b (δ 3.79, 3.87) of Gal were observed, respectively, supporting that the OH-3 group of the anthocyanidin was glycosylated with galactose and also the OH-6 of Gal was glycosylated with rhamnose to form robinobiose (Fig. 1). Consequently, the structure of pigment **2** was determined to be 7-*O*-methylcyanidin 3-*O*-[6-*O*-(α-rhamnopyranosyl)-β-galactopyranoside], which is a new anthocyanin in plants. (Harborne and Baxter, 1999; Williams and Grayer, 2004; Andersen and Jordheim, 2006).

3. Concluding remarks

In this study, two novel 7-*O*-methylanthocyanidin glycosides were found in the flowers of *C. roseus*. Their structures were unambiguously elucidated to be rosinidin 3-robinobioside and 7-*O*-methylcyanidin 3-robinobioside. Therefore, there are three 7-*O*-methylanthocyanidins, hirsutidin, rosinidin and 7-*O*-methylcyanidin found in *C. roseus* of the Apocyanaceae along with malvidin and petunidin as methylanthocyanidin (Filippini et al., 2003). As to the glycosidic pattern, anthocyanin 3-robinobiosides are rather rare in plants and have been reported from only five families, Apocynaceae, Cornaceae, Epacridaceae, Gentianaceae and Polygonaceae (Harborne, 1967; Harborne and Baxter, 1999; Williams and Grayer, 2004; Andersen and Jordheim, 2006). In the Apocynaceae, two anthocyanins, delphinidin 3-robinobioside and delphinidin 3-robinobioside-5-glucoside have been isolated from the flowers of the closely related plant *Vinca major* (Ishikura and Minekishi, 1978). The finding of 3-robinobiosides of rosinidin and 7-*O*-methylcyanidin in *C. roseus* is comparable to the report of *Vinca major*.

4. Experimental

4.1. General procedures

TLC was carried out on plastic coated cellulose sheets (Merck) using nine mobile phases: BAW (*n*-BuOH–

HOAc–H_2O, 4:1:5, upper layer), BuHCl (*n*-BuOH–2 N HCl, 1:1, upper layer), HOAc–HCl (HOAc–HCl–H_2O, 15:3:82), 1% HCl for anthocyanins, Forestal (HCl–HOAc–H_2O, 3:30:10) and formic (HCl–HCO_2H–H_2O, 2:5:3) for anthocyanidins, and BAW, *i*-PrOH–H_2O (4:1), *i*-PrOH–*n*-BuOH–H_2O (7:1:2) and PhOH–H_2O (4:1) for sugars (Harborne, 1984).

Analytical HPLC was performed on a Hitachi 6200 system, using an Inertsil ODS-2 (4.6 φ × 250 mm) column at 35 °C with a flow rate of 0.8 mL/min and monitoring at 520 nm. The eluant was applied as a linear gradient elution for 40 min from 25% to 85% solvent B (1.5% H_3PO_4, 20% HOAc, 25% MeCN in H_2O) in solvent A (1.5% H_3PO_4 in H_2O).

UV–Vis spectra were recorded on UV–Vis multi purpose spectrophotometer (MPS-2450, Shimadzu) in 0.1% HCl–MeOH (from 200 to 700 nm), whereas FAB mass spectra were obtained in the positive ion mode using the magic bullet (5:1 mixture of dithiothreitol and dithioerythritol) as a matrix. NMR spectra were acquired at 500 MHz for ^1H spectra and 125.78 MHz for ^{13}C spectra in DMSO–CF_3CO_2D (9:1) or CD_3OD–CF_3CO_2D (9:1). Chemical shifts are reported relative to a TMS internal standard (δ), and coupling constants are in Hz.

4.2. Plant materials

Seeds of *C. roseus* were purchased from the Sakata Seed Co., Ltd. (Japan). The plants were grown in the experimental farm of Minami-Kyushu University. The fresh flowers were collected in July–October, and dried at 45 °C, and stored in desiccators until needed. The chromaticity value of the fresh flowers of this cultivar, $b/a = 17.83/47.60 = 0.37$ by SE-2000 Spectro Color Meter (Nippon Denshoku Industries Co., Ltd.).

4.3. Isolation of anthocyanins and anthocyanidins

The dried flowers (43 g) were extracted with 5% HOAc (15 L) at room temperature (ca. 20 °C) overnight. Anthocyanins in the extract were adsorbed on a Diaion HP-20 column, and the column was washed with H_2O (5 L). The adsorbed anthocyanins were eluted with MeOH–HOAc–H_2O (75:5:20). After concentration, the eluates were fractionated with Sephadex LH-20 CC using MeOH–HOAc–H_2O (6:1:12). The frs. were further purified with PC (*n*-BuOH–HOAc–H_2O, 4:1:2 and 15% HOAc) and prep. HPLC. Prep. HPLC was performed on a Hitachi 6200 system using an Inertsil ODS-2 column (20 φ × 250 mm) with HOAc solvent. Pigment **1** (23 mg) and pigment **2** (15 mg) were obtained by the process described previously (Toki et al., 2001, 2003).

Acid hydrolysis of pigments **1** and **2** (ca. 7 mg each) was carried out with 2 M HCl (30 mL) at 100 °C for 2 h. After, anthocyanidins **A** and **B** were extracted with *iso*-amyl alcohol (ca. 10 mL), respectively. The *iso*-amyl alcohol extracts were concentrated to dryness. Each anthocyanidin **A** and **B** was purified from the dried extracts by TLC with Forestal. Anthocyanidins **A** and **B** were obtained ca. 4 mg each by this process.

4.4. Analyses of anthocyanins

The identification of anthocyanins was carried out by standard procedures (Harborne, 1984).

4.4.1. 7,3′-O-Dimethylcyanidin (rosinidin A)

Dark red powder; for UV–Vis and TLC, see Table 1; ^1H NMR spectrum, δ 8.80 (1H, *s*, H-4), 8.42 (1H, *m*, H-6′), 8.17 (1H, *br s*, H-2′), 7.39 (1H, *br s*, H-8), 7.21 (1H, *m*, H-5′), 6.86 (1H, *br s*, H-6), 4.02 (1H, *s*, 7-*O*-CH_3 or 3′-*O*-CH_3), 3.98 (1H, *s*, 3′-*O*-CH_3 or 7-*O*-CH_3); HR-FABMS calc. for $C_{17}H_{15}O_6$: 315.0869. Found: 315.0891.

4.4.2. 7-O-Methylcyanidin (B)

Dark red powder; for UV–Vis and TLC, see Table 1; ^1H NMR spectrum, δ 8.74 (1H, *s*, H-4), 8.25 (1H, *br d*, $J = 8.9$, H-6′), 8.22 (1H, *br s*, H-2′), 7.28 (1H, *s*, H-8), 7.12 (1H, *d*, $J = 8.9$ H-5′), 6.87 (1H, *s*, H-6), 4.00 (1H, *s*, 7-*O*-CH_3); HR-FABMS calc. for $C_{16}H_{13}O_6$: 301.0712. Found: 301.0731.

4.4.3. 7,3′-O-Dimethylcyanidin 3-O-robinobioside (rosinidin 3-robinobioside, pigment 1)

Dark red powder; for UV–Vis and TLC, see Table 1; for ^1H and ^{13}C NMR spectra, see Table 2; HR-FABMS calc. for $C_{29}H_{35}O_{15}$: 623.1976. Found: 623.1986.

4.4.4. 7-O-Methylcyanidin 3-O-robinobioside (pigment 2)

Dark red powder; for UV–Vis and TLC, see Table 1; for ^1H and ^{13}C NMR spectra, see Table 2; HR-FABMS calc. for $C_{28}H_{33}O_{15}$: 609.1819. Found: 609.1815.

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