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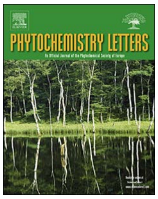

# Phenylphenalenone glycosides: Occurrence, structure revision, and substituent effects on the steric orientation

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ABSTRACT

Glycosides and acyl glycosides of phenylphenalenones, phenylbenzoisochromenones, and structurally related natural products from plants are compiled. With the exception of one naphthalic anhydride glucoside from the Musaceae, all glycosides are chemotaxonomic markers of the Haemodoraceae, subfamily Haemodoroideae. NMR spectroscopic data indicate that in 6-*O*-glycosides of phenylphenalenones and phenylbenzoisochromenones, the substituents at C-5 and C-7 impede rotation of the interjacent sugar moiety at C-6. Furthermore, the structure of the acyl substituent at the C-6" hydroxyl group of some glucosides, previously reported as an allophanyl unit, in this review has been revised to a malonyl unit.

## 1. Introduction

Phenylphenalenones, phenolic natural products mainly occurring in the Haemodoraceae and Musaceae, have recently attracted attention because plants use these to defend themselves against microorganisms (Ot & lvaro et al., 2007; Hidalgo et al., 2016) and nematodes (Hölscher et al., 2014). Most of the phenylphenalenones, phenylbenzoisochromenones ("oxaphenylphenalenones"), and other related structures – in this overview, collectively referred to as phenylphenalenones – occur as aglycones, but some of these compounds have been found in glycosidic form. Here, the currently known phenylphenalenone glycosides from plants are compiled, spectroscopic properties are discussed as a consequence of steric hindrance, and the allophanyl substituent previously reported as an acyl unit attached to the glucose moiety of some of the structures has been revised to the malonyl unit.

## 2. Early phenylphenalenone glycosides

In 1955, a unique glycoside was isolated from the Australian plant *Haemodorum corymbosum* (Cooke and Segal, 1955a) and named haemocorin. The carbohydrate unit was reported to be cellobiose, and degradative studies identified the aglycone as dihydroxymethoxy-phenylperinaphthenone (Cooke and Segal, 1955b; Cooke et al., 1958), later called 2,6-dihydroxy-5-methoxy-9-phenyl-1*H*-phenalen-1-one (**1a**: $R^1$ = H) (Cooke and Edwards, 1981) (Fig. 1). However, haemocorin aglycone may also occur as a tautomeric structure, 5,6-dihydroxy-2-methoxy-7-phenyl-1*H*-phenalen-1-one (**1b**: $R^2$ = H). Notably, substitution at the hydroxyl group in position 6 of **1a** and **1b** but not position 2 of **1a** would prevent tautomerization. Thus, it seems possible that the sugar unit of haemocorin occupies different positions, and indeed, some of these have been depicted in the literature (Fig. 1) (Cooke and Edwards, 1981; Dias et al., 2009; Edwards and Weiss, 1974; Laundon and Morrison, 1971; et al., 1969). However, haemocorin should be re-isolated in order to obtain NMR spectroscopic evidence of the structure.

Lachnanthoside, another phenylphenalenone bioside, was isolated from *Lachnanthes tinctoria* and the structure assigned to **2a** (Edwards and Weiss, 1974). Acid hydrolysis of this compound released only glucose, and, using chromatographic methods, the authors excluded cellobiose, the diglucose moiety of haemocorin, as a carbohydrate. The analysis of $^1$H NMR chemical shifts led to the suggestion that the biosyl unit was attached to position 6.

However, the chemical shift of $\delta$ 8.46 reported for H-7 of lachnanthoside (**2a**) is very close to $\delta$ 8.47, which was the value of the chemical shift determined for the corresponding proton (H-9) of 6-*O*-[6"-*O*-malonyl-ß-D-glucopyranosyl-2,5-dihydroxy-7-phenylphenalen-1-one (**3**). Compound **3** was isolated from *Wachendorfia thyrsiflora* (Fang et al., 2012) and *Xiphidium caeruleum* (Chen et al., 2017). Based on the similarity of these chemical shift values, the structure of lachnanthoside likely has to be revised as 2,5-dihydroxy-6-*O*-biosyl-7-phenylphenalen-1-one (**2b**) (Fig. 1). Hence, the structure of lachnanthoside may differ from that of haemocorin only in the 2-*O*-methyl group and in the link between the glucose units of the biosyl moiety. Unfortunately, *L. tinctoria*, the source of lachnanthoside, was unavailable to us. Thus, until now, it has been impossible to re-isolate the glycoside to confirm the suggested revised structures and to identify its biosyl moiety using

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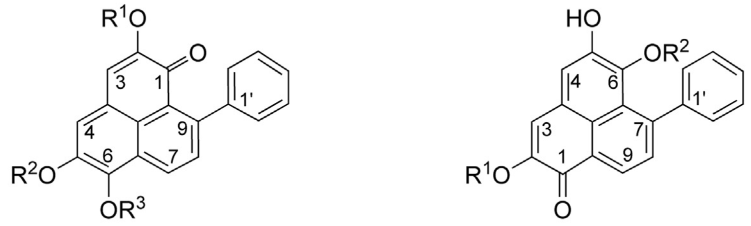


**1a:** R$^1$ = cellobiosyl, R$^2$ = CH$_3$, R$^3$ = H
**2a:** R$^1$ = R$^2$ = H, R$^3$ = unknown biosyl

**1b:** R$^1$ = CH$_3$, R$^2$ = cellobiosyl
**2b:** R$^1$ = H, R$^2$ = unknown biosyl

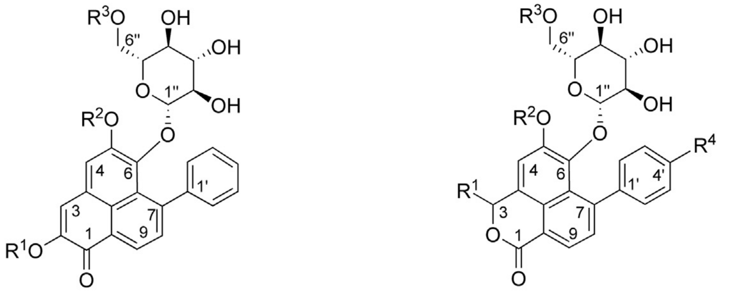
**Fig. 1. 1a**: Structure of haemocorin as shown by Weiss and Edwards (1969), Edwards and Weiss (1974); and Dias et al. (2009). **1b**: Structure of haemocorin as shown by Laundon and Morrison (1971); and Cooke and Edwards (1981); **2a**: Structure of lachnanthoside as reported by Edwards and Weiss (1974). **2b**: Structure of lachnanthoside as suggested in this work by comparing NMR data with related phenylphenalenone glycosides.

modern NMR methods.

## 3. 6-*O*-Glycosides of phenylphenalenones and phenylbenzoisochromenones

### 3.1. *Structure and occurrence*

Further phytochemical studies of Haemodoraceae species resulted in the isolation of dilatrin (**4**) and lachnanthoside aglycone 1-glucoside (**4**) (Dora et al., 1993) (Fig. 2). The aglycones of **4** and **5** have a 7-phenylphenalenone scaffold and are identical with those of **1b** and **2b**, respectively. Both compounds have attached the carbohydrate unit to the hydroxyl group in position 6. The methylation of compounds **3** and **4** with diazomethane in both cases afforded monomethyl dilatrin (**6**) as a semi-synthetic derivative. Investigation of the polar fractions of *X. caeruleum* revealed the occurrence of two further phenylphenalenone glycosides, compounds **7** and **8**, which differ from dilatrin (**4**) and lachnanthoside aglycone 1-glucoside (**5**) only by an additional substituent in position 6” of the glucosyl moiety (Fig. 2). HMBC correlations of the methylene protons ($H_2$-6”) of the glucose with an ester carbonyl established the presence of a substituent in that position. Identification of the ester component appeared problematic because no $^1$H NMR signals assignable to this moiety were observed. Thus, based on mass spectrometric analysis and transesterification experiments, this substituent was suggested to be an allophanyl moiety (Opitz et al., 2002). Further investigations of these compounds were carried out to explore their organ- and cell-specific distribution in *X. caeruleum* (Opitz and Schneider, 2002; Opitz et al., 2003; Schneider et al., 2005) and to study their occurrence (Fang et al., 2011), biosynthesis (Brand et al., 2006; Munde et al., 2013) and oxidative conversion in *W. thyrsiflora* (Opitz and Schneider, 2003). For biosynthetic purposes, the 2,5-di-$O^{13}CH_3$ derivative **9** was prepared from compound **7** by methylation with [$^{13}$C]-diazomethane. During our research on phenylphenalenone glycosides, liquid chromatography-photodiode array detection-solid phase extraction-nuclear magnetic resonance spectroscopy (LC-PDA-SPE-NMR) was used (Fang et al., 2012). Under such conditions, the NMR spectra were measured immediately after elution from the post-column SPE cartridges. This procedure was slightly different from the conventional procedure, in which the dissolved samples are awaiting NMR measurements in an autosampler queue. Hence, under SPE-NMR conditions, the C-H/C-D exchange by MeOH-$d_4$ was sufficiently retarded to allow for the detection of NMR signals of an additional methylene group. Signals at $\delta_H$ 3.0–3.2/$\delta_C$ 41 in the $^1$H-, $^{13}$C NMR and HSQC spectra suggested a malonyl instead of an allophanyl unit. HMBC correlations confirmed the substituent at 6”-OH to be malonyl. Hence, we have to conclude that compounds **7** to **9** do not exist and their structures have to be revised to malonyl glucosides **3**, **10** and **11** (Fig. 2). HRMS data are also consistent with the structures of malonyl



**3:** R$^1$ = R$^2$ = H, R$^3$ = malonyl
**4:** R$^1$ = CH$_3$, R$^2$ = R$^3$ = H
**5:** R$^1$ = R$^2$ = R$^3$ = H
**6:** R$^1$ = R$^2$ = CH$_3$, R$^3$ = H
**7:** R$^1$ = CH$_3$, R$^2$ = H, R$^3$ = allophanyl
**8:** R$^1$ = R$^2$ = H, R$^3$ = allophanyl
**9:** R$^1$ = R$^2$ = CH$_3$, R$^3$ = allophanyl
**10:** R$^1$ = CH$_3$, R$^2$ = H, R$^3$ = malonyl
**11:** R$^1$ = R$^2$ = CH$_3$, R$^3$ = malonyl
**12:** R$^1$ = H, R$^2$ = CH$_3$, R$^3$ = malonyl

**13:** R$^1$ = R$^2$ = H, R$^3$ = allophanyl, R$^4$ = H
**14:** R$^1$ = H, R$^2$ = CH$_3$, R$^3$ = allophanyl, R$^4$ = H
**15:** R$^1$ = R$^2$ = H, R$^3$ = malonyl, R$^4$ = H
**16:** R$^1$ = H, R$^2$ = CH$_3$, R$^3$ = malonyl, R$^4$ = H
**17:** R$^1$ = R$^2$ = H, R$^3$ = malonyl, R$^4$ = OH
**18:** R$^1$ = R$^2$ = R$^3$ = R$^4$ = H
**19:** R$^1$ = R$^2$ = R$^3$ = H, R$^4$ = OH
**20:** R$^1$ = H, R$^2$ = CH$_3$, R$^3$ = R$^4$ = H
**21:** R$^1$ = COOH, R$^2$ = R$^3$ = R$^4$ = H

**Fig. 2. 3** to **12**: Structures of phenylphenalenone-6-*O*-glycosides reported in the literature. **13** to **21**: Structures of phenylbenzoisochromenone-*O*-glycosides reported in the literature. The structures of allophanyl glycosides **7** to **9**, **13** and **14** are revised here to the corresponding malonyl glycosides **3**, **10**, **11**, **15**, and **16**.