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SYNTHESIS AND STRUCTURE PROOF OF MORINDONE 6-*O*-PRIMEVEROSIDE AND 6-*O*-RUTINOSIDE

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Key Word Index—*Morinda*; Rubiaceae; anthraquinone glycosides; morindone biosides; synthesis; structure proof.

Abstract—The naturally occurring 1,5-dihydroxy-2-methyl-6-*O*-β-primeverosyl- and 6-*O*-β-rutinosyl-anthraquinones were synthesized and their structures thereby confirmed.

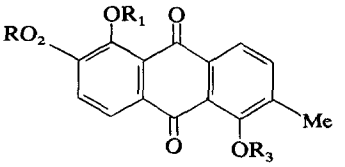
Several biosides of morindone (1,5,6-trihydroxy-2-methylanthraquinone) (**1**) have been isolated from different plants [1–13], especially from those belonging to the genus *Morinda* (Rubiaceae) [14]. They have all been given the name 'morindin' but only three have been identified: namely the 6-β-primeveroside (**4**) from *M. persicaefolia* [9], *M. tinctoria* var. *tomentosa* [12], and *M. lucida* Benth. [14], the 6-β-rutinoside (**7**) from *Coprosma australis* [8, 11] and one from *M. tinctoria* [10] which was called the 6-β-gentianoside being probably the gentiobioside.

The sugar moiety was assumed in all cases to be linked to the C-6 hydroxyl group either because the glycosides were resistant to mild methylation or because vigorous methylation followed by hydrolysis gave morindone 1,5-dimethyl ether (**2**) [10, 12]. The structure of the sugar units was identified after hydrolysis by cochromatography with authentic samples [10, 11] or in one case [12], by permethylation and subsequent hydrolysis. Although the above-mentioned sugars occur frequently in combination with hydroxylated anthraquinoses [14], the studies did not prove the configuration of the glycosidic linkages.

Demagos [13] investigated morindone 6-β-primeveroside isolated from *Morinda lucida* by ^{1}H NMR spectroscopy at 270 MHz and established the presence of a β-glycosidic linkage between both glucose and aglycone and also between xylose and glucose. No proof has been provided as yet for the position of the inter-sugar linkage. Further, the mp and $[\alpha]_D$ of the sample investigated by him differed from data given for morindone 6-primeverosides isolated earlier [10, 12].

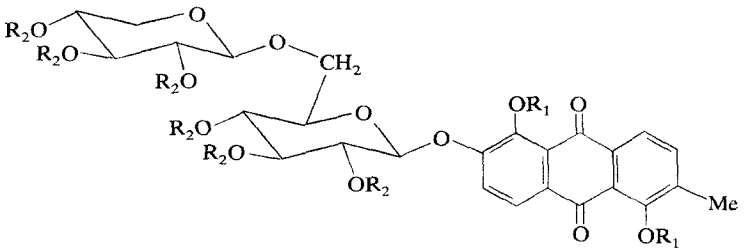
For definite structure proof, we have synthesized morindone 6-*O*-β-primeveroside (**4**) and 6-*O*-β-rutinoside (**7**). The aglycone morindone was synthesized according to Jacobson and Adams [15] starting from opianic acid and 4-bromo-2-methylphenol. It has to be noted that the mp of key intermediate, 1,2-di-*O*-methylmorindone (**3**), differed from reported values [13, 15, 16]. Demethylation of **3** gave morindone (**1**).

Of the three free hydroxyl groups of morindone (**1**), as shown earlier [17], the non-chelated one at C-6 seems to be the most reactive in glycosidic coupling. α-Primeverose-hepta-*O*-acetate was prepared according to McCloskey and Coleman [18], the bromination being carried out with HBr in acetic acid under very mild conditions. Glycosidation of morindone (**1**) with α-acetobromoprimeverose in pyridine using Ag_2CO_3 gave negligible yields. Glycosidation in acetone in the presence of KOH, a method first used with anthraquinones by Zemplén and Bognár [19], not only gave higher yields but permitted the recovery of unreacted aglycone. The product (**5**) was deacetylated with NaOMe in MeOH to yield **4** identical in every respect with an authentic sample of 'morindin' isolated from *M. tinctoria* var. *tomentosa* [12].

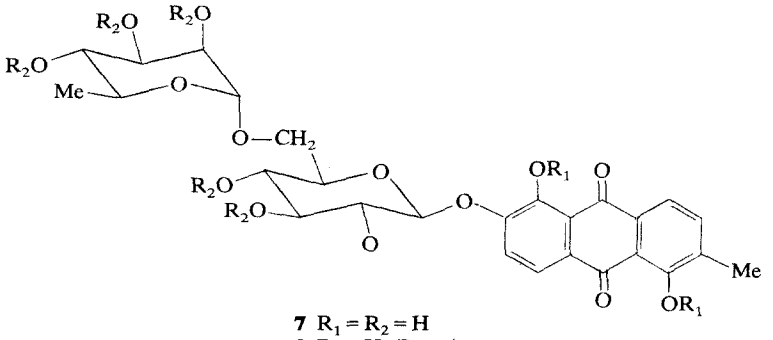


1 $R_1 = R_2 = R_3 = H$
2 $R_1 = R_3 = Me$; $R_2 = H$
3 $R_1 = R_2 = Me$; $R_3 = H$

Reaction of morindone (**1**) with α-acetobromorutinose [20] in pyridine in the presence of Ag_2CO_3 was satisfactory and the product gave, after deacetylation, morindone 6-*O*-β-rutinoside (**7**) of mp 169–171° instead of the reported value of 264°. The structure of **7** was confirmed also by the ^{1}H NMR and ^{13}C NMR spectra of the acetate **9**. The discrepancy in mps was later resolved by carefully observing the melting behaviour of synthetic **7**, and a sample of 'morindin' isolated by Briggs and LeQuesne from *Coprosma australis* [11]. Under the microscope, both compounds melted at 168–171°, then resolidified and finally gradually decomposed from 260° onwards. In the decomposition product, morindone was detected by TLC and the second mp observed was actually that of impure morindone.



4 $R_1 = R_2 = H$
5 $R_1 = H$; $R_2 = Ac$
6 $R_1 = R_2 = Ac$



7 $R_1 = R_2 = H$
8 $R_1 = H$; $R_2 = Ac$
9 $R_1 = R_2 = Ac$

EXPERIMENTAL

Mps were taken on a Kofler microhotstage and are uncorr. IR spectra were recorded as KBr pellets, NMR spectra at 60 and 100 MHz for ^1H and 23.5 MHz for ^{13}C with TMS as internal standard. Column chromatography was performed on Si gel and TLC on Merck plates. Solvent systems: (A) toluene–Me_2CO–HOAc (10:1:1); (B) EtOAc–MeOH–H_2O (100:16.5:13.5); (C) toluene–EtOH (9:2). Morindone (**1**) was prepared via the 1,2-di-*O*-methyl-ether (**2**), as described by Jacobson and Adams [15]; here only mps and as yet unrecorded spectral data are reported.

1,2-*Di-O-methoxy-5-hydroxy-6-methyl-9,10-anthracenedione* (**2**). Yellow needles (from toluene) mp 242–244° (lit. [15] 138.5–139°, lit. [13] 257–259°). UV (EtOH)nm: 225, 265, 283, 292, 411. IR cm^{-1}: 1665, 1620 (CO). ^1H NMR (in DMSO-d_6): δ 2.23 ppm (3H, Me), 3.82 (3H, OMe), 3.98 (3H, OMe), 7.5 (3H, H-3,4,7), 7.9 (1H, *d*, $J = 8$ Hz, H-8), 14.84 (1H, OH).

1,5,6-*Trihydroxy-2-methyl-9,10-anthracenedione, morindone* (**1**). Mp 282–284° (from toluene) (lit. [14] 281–282°). UV (EtOH) nm: 233, 262, 291, 300 and 445. IR cm^{-1}: (CO). ^1H NMR (in DMSO+TFA): δ 2.28 (3H, Me), 7.2 (1H, *d*, $J = 9$ Hz, H-7), 7.6 (2H, H-3,4), 7.74 (1H, H-8).

1,5-*Dihydroxy-2-methyl-6-O-β-primeverosyl-9,10-anthracenedione* (**4**). To a soln of morindone (**1**) (200 mg) and α-acetobromoprimeverose (600 mg) in Me_2CO (30 ml) a soln of KOH (150 mg) in H_2O (17 ml) was added dropwise. After stirring for 2 hr, Me_2CO was evapd, and the residue extracted with $CHCl_3$, washed with H_2O and evapd. To the residue MeOH (10 ml) was added to ppt. the unchanged aglycone (70 mg). After filtration and evapn the residue was deacetylated and purified by column chromatography (solvent B). Subsequent crystallization from 66% EtOH gave yellow needles (58 mg, 14%), mp 257–259° (lit. [12] 244–247°, lit. [13] 215–220°). The mmp with an authentic sample [12] was undepressed. $[\alpha]_D^{25} -87.3°$ (*c* 0.60 in dioxane). (Found: C, 55.24; H, 4.72. $C_{26}H_{28}O_{14}$ requires: C, 55.32; H, 4.99%). UV (EtOH) nm: 232, 262, 290, 300, 445. IR cm^{-1}: 1625 (CO). The IR spectra of the two samples were superimposable.

1,5-*Di-O-acetyl-2-methyl-6-O-(hexa-O-acetyl-β-primeverosyl)-9,10-anthracenedione* (**6**). **4** was acetylated with Ac_2O in Py and worked up as usual to yield the octa-*O*-acetate (**6**) as pale yellow needles from HOAc, mp 252–256° (lit. [12] 249–251°). The mmp with an authentic sample was undepressed. $[\alpha]_D^{25} -99.8°$ (*c* 1.01 in dioxane). (Found: C, 55.72; H, 4.71. $C_{42}H_{44}O_{22}$ requires: C, 56.00; H, 4.92%). UV (EtOH) nm: 261, 284 360. IR cm^{-1}: 1675, 1760 (CO). ^1H NMR (in $CDCl_3$): δ 1.88 (18H, sugar Ac), 2.33 (3H, Me), 2.45, 2.54 (6H, C_1-Ac, C_5-Ac), 3.7–5.3 (12H, sugar protons), 7.25–7.5 (4H, H-3,4,7,8).

1,5-*Dihydroxy-2-methyl-6-O-β-rutinosyl-9,10-anthracenedione* (**7**). To a soln of morindone (**1**) (200 mg) in Py (10 ml) at 0° Drierite (500 mg) and Ag_2CO_3 (360 mg) were initially added and subsequently followed by a solution of acetobromorutinose (280 mg) in Py (5 ml). After stirring for 3 hr at room temp. with the exclusion of moisture and light, the mixture was diluted with $CHCl_3$ (40 ml), filtered, extracted with 5% HCl and washed with H_2O. After evapn a soln of the crude product in MeOH (10 ml) was treated with M NaOMe (10.5 ml) at room temp. for 24 hr and subsequently acidified to pH 6 with HOAc. After evapn the crude product was purified by column chromatography (solvent B) to yield yellow needles from HOAc, 121 mg (28%), mp 169–171° (lit. [11] coalesced and resolidified at 170–173°, melted at 264.5°). The authentic sample [11] melted at 164–167°, undepressed by **7**. (Found: C, 55.24; H, 4.72.

$C_{27}H_{30}O_{14}$ requires: C, 56.05; H, 5.22%). UV (EtOH) nm: 230, 259, 285, 436. IR cm^{-1}: 1665, 1740 (CO). IR spectra of the synthetic and natural samples were superimposable.

1,5-*Di-O-acetyl-2-methyl-6-O-(hexa-O-acetyl-β-rutinosyl)-9,10-anthracenedione* (**9**). **7** was acetylated as described for **6** to give, after chromatography (solvent C), the octa-*O*-acetate (**9**) as a pale yellow amorphous powder, mp 129–134°. (Found: C, 56.11; H, 5.12. $C_{43}H_{46}O_{22}$ requires: C, 56.45; H, 5.06%). UV (EtOH) nm: 212, 255, 340; IR cm^{-1}: 1665 (CO). ^1H NMR (in $CDCl_3$): δ 1.18 (3H, *d*, $J = 6$ Hz, rhamnose-Me), 2.04 (18H, sugar-Ac), 2.29 (3H, Me), 2.40, 2.42 (6H, C_1-Ac, C_5-Ac), 3.8 (4H, glucose H-5,6,6 and rhamnose H-5), 4.75 (1H, rhamnose H-1), 5.2–5.5 (7H, glucose H-1,2,3,4 and rhamnose H-2,3,4), 7.31 (1H, 7-H, overlapped by $CHCl_3$ peak), 7.61 (1H, *d*, $J = 8$ Hz, H-3), 8.04 and 8.20 (2H, *d*, $J = 8$ and 9 Hz, H-4,8). ^{13}C NMR (in $CDCl_3$): δ 16.63, 17.39 (C-$\underline{C}H_3$), 20.41, 20.55, 20.58, 20.66, 20.74, 20.71, 20.99 (CO$\underline{C}H_3$), 66.56, 66.94, 68.90, 68.98, 69.49, 70.54, 70.88, 72.31, 72.91 (sugar-C-C), 98.16, 98.51 (sugar C_1), 119.54, 125.27, 127.46, 128.35, 129.89, 134.23, 136.27, 139.29, 148.36, 153.58 (aromatic C), 168.79, 168.82 169.03 169.41, 169.87, 169.95, 169.97, 170.02 ($\underline{C}OMe_3$), 180.51, 181.01 (9,10-$\underline{C}O$).

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