A Quinol Glucoside Isolated from *Cornus* Species

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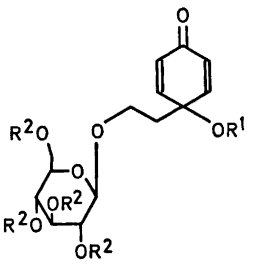
A glucoside, with a chemical structure novel in type to constituents of higher plants, has been isolated by column chromatography from an aqueous, flavonoid-free extract of autumn foliage of the North American dogwood *Cornus femina* Miller. The non-crystalline glucoside, $C_{14}H_{20}O_8$, has been assigned the structure *1* on the following evidence.

UV, [λ_{max} (EtOH) 227 nm (ε 9400)]; IR, [λ_{max} (KBr) 1618, 1663 cm^{-1}], and ^1H NMR data (see Experimental) were



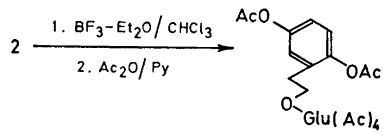
1 $R^1 = R^2 = H$

2 $R^1 = H, R^2 = Ac$

3 $R^1 = R^2 = Ac$

all in accord with those expected for structure *1*.* Acetylation, with Ac_2O in pyridine, afforded a tetraacetate *2*, and a pentaacetate *3*, both syrupy, exhibiting, as parts of their ^1H spectra, signals virtually coinciding with those of methyl tetra-*O*-acetyl-β-D-glucopyranoside, save for the anomeric proton. Emulsin-catalyzed hydrolysis of *1* proceeded easily to give glucose and the aglucone, isolated as the non-crystalline diacetate *4*, exhibiting the expected NMR signals.

Additional chemical evidence in support of structure *1* was provided by BF_3-induced rearrangement [2] of *2* to give, after acetylation, the expected hydroquinone glucoside acetate *5*, as colourless crystals. Similarly, acid-catalyzed hydrolysis of *1*,



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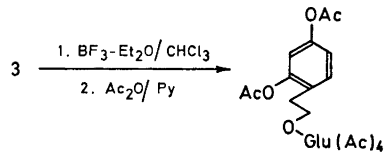


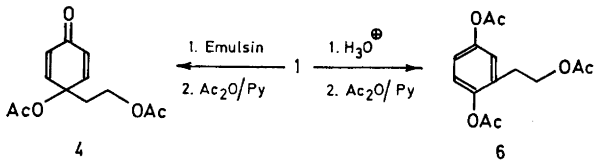
7

followed by acetylation, afforded homogentisyl triacetate *6* as the major product. On treatment with BF_3-etherate in $CHCl_3$, *3* underwent quinol ester-phenol rearrangement [2] to give, after acetylation, the resorcinol glucoside acetate *7*.

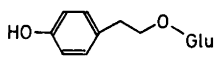
The genus *Cornus* (*sensu* Wangerin) comprises 46 species, 32 of which compose the subgenus *Thelycrania* Endl.[3] In the present work, 17 of the latter were studied and invariably found to contain *1*. Conversely, none of 7 studied species, belonging to 4 other subgenera,[3] contained *1* in detectable amounts. Taxonomically interesting, the occurrence of *1* and of iridoid glucosides, studied in parallel on the 24 *Cornus* species, appears to be mutually exclusive.

Salidroside, *8*, formerly known from species of *Salix* [4] and several other genera,

* 4-Hydroxy-4-methyl-cyclohexa-2,5-dienone exhibits absorption maxima at λ 226 nm (ε 17 760) (EtOH) in the UV,[1] and at 1617 and 1673 cm^{-1} ($CHCl_3$) in the IR region.[2]



4 6



8

was consistently encountered as a minor congener of *1*.

A full account of the distribution of *1* and iridoids within the *Cornus* group will appear elsewhere.

Experimental. Ultraviolet spectra were measured in EtOH; ^{1}H NMR spectra were recorded on a Varian HA-100 instrument in $CDCl_3$-solution with TMS as an internal reference, when not otherwise indicated. For TLC, silica gel PF_{254} (Merck) was employed; preparative separations were performed on 20 × 40 cm plates, coated with 1 mm thick layers of silica gel. Detection in UV light.

Isolation of glucoside 1. Frozen foliage (350 g) of *C. femina* (collected in September 1971 and stored at −28° in polyethylene bags) was homogenized in ethanol (1.0 l). After filtration, the filter cake was treated similarly with another 0.5 l portion of ethanol. The combined filtrates were concentrated *in vacuo* to 150 ml. The remaining solution was extracted with two 500 ml portions of ether. The ether solutions were discarded. The aqueous phase was filtered through a column of alumina (300 g),[5] followed by washing of the column with water (1 l). The combined filtrates were passed through a filter bed of charcoal (175 g) and Celite (200 g), placed in a 22 cm Büchner funnel. The adsorbed glycosides were washed free of carbohydrates with 4 l of water. Elution with 50 % EtOH (2 l) and then 66 % EtOH (0.75 l), followed by concentration of the eluates *in vacuo*, afforded a crude glycoside fraction (5.7 g).

Repeated column chromatography on silica gel, with BuOH:MeOH:H_2O (7:1:3) as the mobile phase, yielded a fast-running glycoside (fraction a, see below) in addition to the sirupy, chromatographically homogeneous glycoside *1* (3 g). After thorough drying (over P_2O_5), the material was used for further characterization: $[\alpha]_D^{22}$ − 23° (*c* 1.6, EtOH); the ^{1}H NMR spectrum (in D_2O, TMS as external reference) exhibited signals at: 7.44 and 6.59 (4H, vinylic, composing an AA'BB' system; J_{AB} 10.5 Hz), 4.71 (1H, anomeric proton H-1', d, *J* 7 Hz), 2.48 (2H, t, *J* = 7 Hz), and 3.40 − 4.50 ppm (8H, consisting of 2H from the aglucone, and the 6 non-anomeric, carbon-bound protons of the glucose moiety).

Acetates of 1. Acetylation of *1* (1.0 g) was performed in pyridine (10 ml) with acetic anhydride (5 ml) at room temperature. After 18 h, work-up in the usual way yielded a mixture of two acetates (1.39 g), separated on chromatography (in ether) into a slow- and a faster-running component.

The former, consisting of *2* (203 mg), was thoroughly dried before analysis. (Found: C 52.35; H 6.20. Calc. for $C_{22}H_{28}O_{12}$: C 52.17; H 6.13). $[\alpha]_D^{22}$ − 26° (*c* 3.6; EtOH); λ_{max} 227 nm (ε 10 600); NMR-data: 6.92 and 6.16 (2 × 2H, vinylic), 5.40 − 4.90 (3H; H-2', H-3', H-4'), 4.56 (1H, H-1', d, *J* 7.5 Hz), 4.27 and 4.23 (2H, H-6'), 4.08 and 3.71 (2 × 1H; A and B part of an ABX_2-system), *ca* 3.75 (1H, H-5'), 3.37 (1H, O*H*), and 2.13 − 2.00 ppm (14H, 4 OAc plus CH_2).

The pentaacetate, *3* (532 mg), was analyzed after drying. (Found: C 54.57; H 5.59. Calc. for $C_{24}H_{30}O_{13}$: C 54.75; H 5.74). $[\alpha]_D^{22}$ − 18.0° (*c* 2.0; EtOH); λ_{max} 239 nm (ε 9800). NMR-data: 6.90 and 6.28 (4H, vinylic), 5.35 − 4.85 (3H; H-2', H-3', H-4'), 4.52 (1H, H-1', d, J 7.5 Hz), 4.28 and 4.23 (2H, H-6'), 3.99 and 3.61 (each 1H; A and B part of an ABX_2-system, J_{AB} 10.5 Hz, $J_{AX} = J_{BX} = 6$ Hz), *ca.* 3.75 (1H, H-5'), 2.18 (2H, t, X_2-part of an

ABX_2-system), and 2.15–2.03 ppm (15H; 5 OAc).

Enzymic hydrolysis of 1. A mixture of *1* (408 mg), emulsin (190 mg), and water (10 ml) was stirred overnight at room temperature. The filtered solution was extracted with three 10 ml portions of BuOH; the solvent was removed *in vacuo*, and the residue was subjected to acetylation (with Ac_2O in pyridine). From the resulting product mixture (175 mg), a homogeneous, non-crystalline product, consisting of *4*, was isolated by chromatography with C_6H_6:Et_2O (1:1) as the mobile phase. (Found: C 60.38; H 5.82. Calc. for $C_{12}H_{14}O_5$: C 60.50; H 5.92.) λ_{max} 239 nm (ε 7100); NMR-data: 6.88 and 6.28 (each 2H, composing an AA'BB'-system), 4.18 (2H, t, *J* 6.5 Hz), 2.19 (2H, t, *J* 6.5 Hz), 2.08 and 2.03 ppm (2×3H; 2 OAc).

In the above aqueous solution, the presence of glucose was demonstrated by paper-chromatographic analysis and comparison with an authentic specimen, in (i) BuOH:EtOH:H_2O (4:1:3), and (ii) BuOH:Py:H_2O (6:4:3).

Rearrangement of 2. A solution of the tetra-acetate *2* (250 mg) in $CHCl_3$ (5 ml) was treated with BF_3,Et_2O (150 mg) for 3 h at room temperature. An excess of $NaHCO_3$-solution was added, and the mixture was extracted with $CHCl_3$. The crude reaction product (270 mg) was purified by chromatography (ether as an eluent) to give the rearranged product (131 mg). Acetylation, with Ac_2O in pyridine, afforded the hexaacetate *5* (157 mg), which was recrystallized from MeOH, m.p. 136–137.5°. (Found: C 54.94; H 5.76. Calc. for $C_{26}H_{32}O_{14}$: C 54.92; H 5.67) $[\alpha]_D^{22}$ −16.0° (*c* 3; $CHCl_3$). λ_{max} 267 (ε 600) and 272 nm (ε 560). NMR-data: 7.0 (3H, s, arom.), 2.81 (2H, t, *J* 7 Hz, benzylic CH_2), 2.31 and 2.29 (2×3H, phenolic OAc); 2.09, 2.02, 1.99, and 1.96 ppm (4×3H, aliphatic OAc).

Rearrangement of 3. The pentaacetate *3* (129 mg) was dissolved in CH_2Cl_2 (10 ml), and two drops of BF_3,Et_2O were added. After 5 min at room temperature, the solution was washed with two 5 ml portions of a $NaHCO_3$-solution. After drying, and concentration to dryness, the residue was reacetylated (Ac_2O in pyridine) to give a mixture of products (99 mg), from which *7* was isolated as the major product (66 mg) by chromatography in Et_2O. (Found: C 55.01; H 5.55. Calc. for $C_{26}H_{32}O_{14}$: C 54.93; H 5.67.) $[\alpha]_D^{22}$ −11° (*c* 2.1, EtOH); λ_{max} 266 (ε 560) and 271 nm (ε 580). NMR-data: 7.26 (1H, dd, *J* 9 Hz and *ca.* 1 Hz, arom.), 7.01–6.88 (2H, arom.), 2.83 (2H, t, *J* 6.5 Hz, benzylic CH_2), 2.32 and 2.27 (2×3H, phenolic OAc), and 2.10–1.95 ppm (4×3H, aliphatic OAc).

Acid hydrolysis of 1. The glucoside *1* (138 mg) was dissolved in 3 % H_2SO_4 (5.5 ml) and heated on a steam-bath for 48 h. Ether extraction (5×10 ml) afforded the aglucone (34 mg), which was subjected to acetylation (Ac_2O in pyridine) for 2 h at r.t. and worked up in the usual way to give a crude product (43 mg), which was purified by chromatography (pentane-ether, 5:2) to give a homogeneous specimen (30 mg) of homogentisyl acetate *6*. (Found: C 60.08; H 5.76. Calc. for $C_{14}H_{16}O_6$: C 59.99; H 5.75.) λ_{max} 217 (ε 5500), 268 (ε 575), and 273 nm (ε 550). NMR-data: 7.09 (3H, s, arom.), 4.28 (2H, t, *J* 7.5 Hz), 2.89 (2H, t, *J* 7.5 Hz, benzylic CH_2), 2.34 and 2.29 (2×3H, phenolic OAc), and 2.04 ppm (3H, aliphatic OAc).

Isolation of salidroside, 8. Fraction a, from the glucoside isolation, was freed of less polar contaminants by extraction with three 50 ml portions of EtOAc. The aqueous solution was taken to dryness *in vacuo*, and the residue was subjected to acetylation (Ac_2O, pyridine, 2 days). Repeated chromatography (Et_2O as the eluent) gave a fraction (98 mg) which, according to NMR analysis, was rich in salidroside acetate. Deacetylation, with NH_3 in MeOH, yielded a crude glucoside, which was purified by chromatography (in $CHCl_3$:MeOH, 4:1) to give a homogeneous fraction. On trimethylsilylation a product was formed, possessing an NMR-spectrum, indistinguishable from that of persilylated salidroside.[6]

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