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Quercetin-7-neohesperidoside: synthesis and properties

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Summary. Quercetin-7-neohesperidoside was prepared from eriodictyol 7-neohesperidoside by alkaline peroxide oxidation. Spectral properties of this compound and its derivatives are reported.

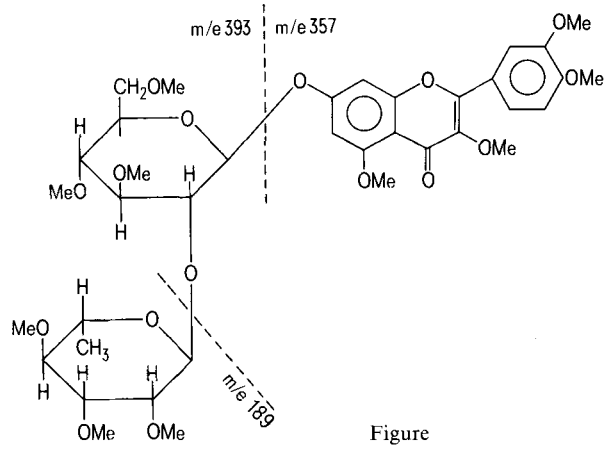
There are 2 major ways for the synthesis of the C_{15} flavonoid skeleton. The one is condensation of a C_6-C_2 unit with a C_6-C_1 unit as described in the scheme. The 2nd is the biomimetic synthesis, the acylation of phenols with cinnamic acid derivatives[1]. We have chosen the 1st method to synthesize quercetin 7-neohesperidoside (**2**), a compound previously not reported to occur in the plant kingdom.

Since the transacylation method[2] gave unsatisfactory results, the synthesis of quercetin 7-neohesperidoside (**2**) was carried out according to the scheme. The intermediate in the synthesis was eriodictyol 7-neohesperidoside (**3**), obtained by the condensation of phloroacetophenone 4-neohesperidoside[3] (**1**) with protocatechualdehyde. We have obtained a greatly improved yield (66%) of **3** by a slight modification of the reported procedures[4,5]. After condensation of phloroacetophenone (**1**) with protocatechualdehyde in the presence of cold aqueous 60% KOH, the reaction mixture was treated with 20% aqueous pyridine at room temperature overnight. This treatment cyclized the primary condensation product, the chalcone derivative (**4**), to the corresponding flavanone (**3**). Compound **3** was purified by polyamide column chromatography with H_2O-MeOH as a linear gradient solvent system, and recrystallized from MeOH/H_2O as white needles, m.p. 189–191 °C. (190–191 °C, 187–190 °C)[4,5].

The so obtained eriodictyol 7-neohesperidoside (**3**) (1.2 g) was converted to the corresponding quercetin derivative (**2**) (0.22 g, 17%) by treating with 2N NaOH/30% H_2O_2 at 0 °C for 2 days, followed by acidification to pH 6 with conc. HOAc and refluxing for 2 h in the presence of $NaHSO_3$[6]. This reaction proceeds in alkaline medium from the chalcone via the dihydroflavonol to the corresponding flavonol (**2**)[7].

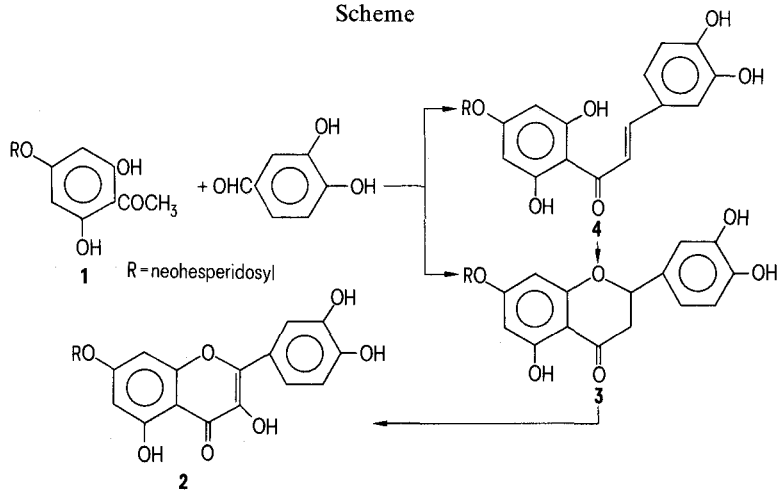
Quercetin 7-neohesperidoside (yellow needles, m.p. 284–286 °C from MeOH/H_2O) was characterized by elemental analysis (calculated: for $C_{27}H_{30}O_{16} \cdot 2\ H_2O$; C, 50.16; H, 5.30; found: C, 50.43; H, 5.39) and spectral data. R_f (cellulose TLC) 0.78 (H_2O), 0.16 (15% HOAc), 0.49 (30% HOAc), 0.51 (1-BuOH-HOAc-H_2O = 4:1:5); UV λ_{max}^{MeOH} nm (log ε) 377 (4.21), 272 sh, 258 (4.31); IR (KBr) ν 3600-3200 (OH), 1650 (C=0) cm^{-1}. As most flavonoid glycosides, underivatized **2** did not exhibit a molecular ion in the mass spectrum because of its low volatility (recorded with a Hewlett-Packard 5985 GC/MS data system, direct insertion probe electron ionization). The compound showed a base peak at m/e 302, contributed by the aglycone (quercetin) ion, where a hydrogen replaced the sugar moiety. Permethylation[8,9] rendered the compound volatile and permitted the recording and interpretation of its mass spectrum. (**2**)-Permethyl ether[10] exibited the molecular ion at m/e 750 with an intensity (27%) characteristic[8] for flavonol 7-glycosides. The principal fragmentation pattern is illustrated in the figure.

Clevage of the glycosidic C-O bond of the terminal sugar (rhamnose) produces the ion at m/e 189 (86%). Successive loss of MeOH from this results in ions at m/e 157 (54%) and 125 (35%). Fission of the glycosidic C-O bond between the sugar (neohesperidoside) and the aglycone gives fragments at m/e 357 and m/e 358 (40%) the latter formed by



Figure

Scheme



hydrogen transfer. Thereafter a CO is lost from the m/e 357 fragment with a simultaneous formation of a phenylbenzofuran derivative at m/e 329 (20%). The neohesperidoside ion appears at m/e 393 (4%). Fragments produced by a retro-Diels-Alder fragmentation are here also of low intensity[9].

Acetylation of **2** with dry pyridine and acetic anhydride at room temperature overnight gave colorless needles (88%), recrystallized from ethanol/water: m.p. 132–134 °C; IR (KBr) ν 1755 (acetyl C=O), 1650 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, 3H, J=6.0 Hz, rhamnose-CH_3), 1.96, 1.98, 2.02, 2.04, 2.12, 2.14 (each singlet for 3H corresponding to acetyl groups at glucose and rhamnose), 2.32 (s, 9H, 3′-, 4′- and 5-OAc), 2.42 (s, 3H, 3-OAc), 3.80–4.28 (m, 5H, glucose-H-2,5,6,6 and rhamnose-H-5), 4.90–5.46 (m, 7H, glucose-H-1,3,4 and rhamnose-H-1,2,3,4), 6.71 (d, 1H, J=2.2 Hz, 6-H), 7.01 (d, 1H, J=2.2 Hz, 8-H), 7.32 (d, 1H, J=8.5 Hz, 5′-H), 7.60–7.72 (m, 2H, 2′- and 6′-H). Anal. calculated for $C_{47}H_{50}O_{26}$: C, 54.76; H, 4.89; found: C, 54.78; H, 4.98.

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Scalarolbutenolide, a new sesterterpenoid from the marine sponge *Spongia nitens*[1]

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Summary. A new sesterterpenoid, scalarolbutenolide *(5)*, has been isolated from the marine sponge *Spongia nitens;* its structure, including the absolute stereochemistry, has been established by chemical and spectroscopic studies.

Previous reports[3–5] from this laboratory described the structures of a variety of terpenes isolated from the marine sponge *Spongia nitens.* Recently we reported[4,5] the isolation and the structures of four tetracarbocyclic sesterterpenes **(1, 2, 3, 4)** all belonging to the series of the scalarinlike[6] compounds. Continuing in this field we now report the full structure of a novel sesterterpenoid **(5),** named scalarolbutenolide.

Extraction of fresh tissues of *S. nitens,* with acetone followed by silica gel fractionation[3] of the ether soluble portion, yielded, in addition to the previously-reported terpenes, crystalline scalarolbutenolide (**5,** 0.005% of dry material, m.p. 220–222 °C, $[\alpha]_D$ ($CHCl_3$)+1.9°, TLC R_f 0.6 light petroleum - diethyl ether (2:8). The structure of scalarolbutenolide **(5)** is based on the following evidence. $C_{27}H_{40}O_5$ (high resolution mass spectrometry); UV (MeOH) 217 (ε, 7.730) nm; IR ($CHCl_3$) 3575, 1735 (acetate), 1750 and 1650 (α,β-butenolide) cm^{-1}; MS 444 (M^+, 2%), 426 (5), 384 (64), 366 (10), 275 (35), 257 (14), 205 (34), 191 (100), 137 (84), 123 (93); PMR ($CDCl_3$) 6.0 (H-20. bs, w/2 3Hz), 5.8 (H-16, m, w/2 5Hz), 4.76 (H-18, bs, w/2 3Hz), 3.80 (H-12, dd, J=4, 1OHz), 2.1 (CH_3CO, s), 0.90 (9H, s), 0.84 (3H, s), 0.68 (3H, s)δ; the CMR data are reported in the table. The mass data, compared with those of the previously described terpenes[4,5], suggest a tetracarbocyclic scalarin-like skeleton for **5,** which also has to contain an acetoxy group and an hydroxy group because of the presence in the mass spectrum of peaks due to consecu-