Synthesis and Taste of Some Isomers of Naringin†

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Naringin (I), a predominant flavonoid of the grapefruit and pummelo, has the structure of naringenin-7-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside] and also has an intense bitterness which is comparable to that of quinine. Horowitz and Gentili¹⁾ mentioned that the point of attachment of L-rhamnose to D-glucose in I is the determining factor of bitterness and substituting other pentoses or hexoses for L-rhamnose will not substantially alter the taste. Recently, Van Niekerk and Koeppen²⁾ synthesized naringenin-7-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-galactopyranoside] (II) which was reported to be as bitter as naringin.

In a previous paper,³⁾ we reported the synthesis of some naringenin-7- β -glycosides and discussed the structure-taste relationships in them.

In this study we newly synthesized four isomers of naringin, namely, naringenin-7-[α -L-quinovopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside] (III), naringenin-7-[β -L-quinovopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside] (IV), naringenin-7-[α -L-quinovopyranosyl-(1 $\rightarrow$ 2)- β -D-galactopyranoside] (V) and naringenin-7-[β -L-quinovopyranosyl-(1 $\rightarrow$ 2)- β -D-galactopyranoside] (VI) by coupling of naringenin (VII) with hexa-O-acetyl- α -L-quinovopyranosyl-(1 $\rightarrow$ 2)- α -D-glucopyranosyl bromide (VIII), hexa-O-acetyl- β -L-quinovopyranosyl-(1 $\rightarrow$ 2)- α -D-glucopyranosyl bromide (IX), hexa-O-acetyl- α -L-quinovopyranosyl-(1 $\rightarrow$ 2)- α -D-galactopyranosyl bromide (X) and hexa-O-acetyl- β -L-quinovopyranosyl-(1 $\rightarrow$ 2)- α -D-galactopyranosyl bromide (XI), respectively, followed by deacetylation. Their tastes were examined in comparison with that of naringin.

As a result, III and V were found to be twice as bitter as I whereas IV and VI were entirely tasteless. From the above organoleptic data the following considerations were made. When α -L-rhamnose unit in I and II is replaced by α -L-quinovose, C₂-epimer of L-rhamnose, the taste is doubled while when replaced by β -L-quinovose the taste becomes null. Accordingly, α -1 $\rightarrow$ 2 linkage in quinovopyranosyl D-glucose and in L-quinovopyranosyl D-galactose is an important factor

to the appearance of bitterness but β -1 $\rightarrow$ 2 linkage in them completely deprives the compounds of their ability to elicit bitter taste. We shall presumably reach the same conclusion in the case of L-rhamnopyranosyl D-glucose in I though the experiment has not yet been carried out because of difficulty of synthesis. In compounds I, II, III and V the vicinal hydroxyl groups at carbon 2 and 3 of L-rhamnose and L-quinovose units have a projected angle of 60°, the former being clockwise and the latter being counterclockwise against hydroxyl group at carbon 3. The fact that III and V maintain the intense bitterness might be ascribed to the Gausche conformation of the above vicinal hydroxyl group of L-quinovose.

EXPERIMENTAL

Mp's, UV, IR and NMR spectra were measured with the same equipment as described in the previous papers.^{3,4)} Thin-layer chromatographic analyses were carried out with silica gel as adsorbent and a mixture of ethyl acetate-methanol-water (80:14:10) as developing solvent. Two percent ferric chloride in ethanol was used as spraying agent.

The taste evaluation of synthesized flavanones was carried out by the same method with five young women as judges.

1) Naringenin-7-[α -L-quinovopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside] (III)

In accordance with the method³⁾ reported by us in the previous paper, naringenin (1.3 g) was coupled with VII in the presence of silver carbonate (1.8 g) and Drierite (2.5 g) in a mixture of chloroform (1.6 ml) and quinoline (16 ml). The condensation product, after deacetylation with 0.4% methanolic sodium methoxide, was purified by column chromatography on silica gel and polyamide columns. III was obtained as needles, mp 180~185°C, in a yield of 288 mg (10.38%). Twice as bitter as I. TLC 0.59. $[\alpha]_D^{25}$ -142° (c =2.66, C₆H₅N). Anal. Found: C, 55.78; H, 5.49; Calcd. for C₂₇H₃₂O₁₄: C, 55.86; H, 5.51%. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (ϵ): 282 (31677), 321 (4980); $\lambda_{\text{max}}^{\text{MeOH-NaOH}}$ nm (ϵ): 238 (sh) (36368), 280 (18138), 424 (33460); $\lambda_{\text{max}}^{\text{MeOH-AlCl}_3}$ nm (ϵ): 254 (14592), 308 (39611), 386 (7842); $\lambda_{\text{max}}^{\text{MeOH-AlCl}_3\text{-HCl}}$ nm (ϵ): 254 (16059), 307 (43263), 386 (7842); $\lambda_{\text{max}}^{\text{MeOH-AcONa}}$ nm (ϵ): 282 (37934), 320 (11440). IR ν cm⁻¹: 3400 (OH), 1650 (C=O).

Acetylation of III with a mixture of acetic anhydride and pyridine gave octaacetate (III'), mp 134~136°C. $[\alpha]_D^{20}$ -88.88° (c =0.72, CHCl₃). Anal. Found: C, 56.31; H, 5.22; Calcd. for C₄₃H₄₈O₂₂: C, 56.33; H, 5.24%. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: acetoxy group: 1.9~2.16 (18H); 2.3, 2.36 (6H, C-5, C-4' acetoxy); aglycon: H-3: 2.66~3.06 (2H, multiplet); H-2: 5.4~5.56 (1H, multiplet); H-6: 6.23 (doublet, J =2 Hz); H-8: 6.46

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(doublet, $J=2$ Hz); H-3', H-5': 7.06 (doublet, $J=8$ Hz); H-2', H-6': 7.40 (doublet, $J=8$ Hz); sugar protons: quinovosyl methyl group: 1.22 (doublet, $J=6$ Hz); 3.6~5.4 (12H).

2) *Naringenin-7-[\beta-L-quinovopyranosyl-(1\rightarrow2)-\beta-D-glucopyranoside] (IV)*

Naringenin was coupled with IX (3.0 g) to afford 0.38 g (13.2%) of IV as an amorphous powder, mp 187~190°C. TLC 0.59. $[\alpha]_D^{15} -37.8^\circ$ ($c=5.0$, C_6H_5N). *Anal.* Found: C, 55.24; H, 5.83; Calcd. for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.51%. UV λ_{max}^{MeOH} nm (ϵ): 224 (30907), 282 (16968), 330 (3009); $\lambda_{max}^{MeOH-NaOH}$ nm (ϵ): 241 (20824), 284 (12019), 418 (15181); $\lambda_{max}^{MeOH-AlCl_3}$ nm (ϵ): 309 (29287); $\lambda_{max}^{MeOH-AlCl_3-HCl}$ nm (ϵ): 307 (23227); $\lambda_{max}^{MeOH-AcONa}$ nm (ϵ): 282 (27875), 322 (6523). IR ν cm^{-1} : 3380 (OH), 1640 (C=O). Acetate (IV'), mp 203~205°C. *Anal.* Found: C, 56.13; H, 5.25; Calcd. for $C_{48}H_{48}O_{22}$: C, 56.33; H, 5.24%. $[\alpha]_D^{15} -30^\circ$ ($c=1.0$, C_6H_5N). NMR $\delta_{Me_4Si}^{CDCl_3}$: acetoxyl group: 1.53~1.93 (18H); 2.21~2.29 (6H, C-5, C-4' acetoxyls); aglycon: H-3: 2.68~2.93 (2H, multiplet); H-2: 5.07 (1H, multiplet); H-6: 6.26 (doublet, $J=2$ Hz); H-8: 6.43 (doublet, $J=2$ Hz); H-3', H-5': 6.97 (doublet, $J=8$ Hz); H-2', H-6': 7.32 (doublet, $J=8$ Hz); sugar protons: quinovosyl methyl group: 1.12 (3H, doublet, $J=6$ Hz), 4.01~4.05 (5H), 4.62~4.90 (7H).

3) *Naringenin-7-[\alpha-L-quinovopyranosyl-(1\rightarrow2)-\beta-D-galactopyranoside] (V)*

Naringenin (0.9 g) was coupled with X to give V in a yield of 0.4 g (20.03%), mp 172°C. TLC 0.59. Twice as bitter as naringin. $[\alpha]_D^{15} -146.4^\circ$ ($c=5.0$, C_6H_5N). *Anal.* Found: C, 53.39; H, 5.63; Calcd. for $C_{27}H_{32}O_{14} \cdot 1(1/2)H_2O$: C, 53.83; H, 5.76%. UV λ_{max}^{MeOH} nm (ϵ): 281 (18900), 331 (3500); $\lambda_{max}^{MeOH-NaOH}$ nm (ϵ): 242 (20500), 282 (13000), 415 (9900); $\lambda_{max}^{MeOH-AlCl_3}$ nm (ϵ): 224 (38100), 307 (19500), 386 (2800); $\lambda_{max}^{MeOH-AlCl_3-HCl}$ nm (ϵ): 224 (36000), 253 (10600), 306 (18400), 383 (3030); $\lambda_{max}^{MeOH-AcONa}$ nm (ϵ): 282 (21400), 332 (4500). IR ν cm^{-1} : 3400 (OH), 1645 (C=O). Acetate (V'), mp 135°C. $[\alpha]_D^{15} -102^\circ$ ($c=1.0$, C_6H_5N). *Anal.* Found: C, 55.54; H, 5.23; Calcd. for $C_{43}H_{48}O_{22} \cdot H_2O$: C, 55.24; H, 5.35%. NMR $\delta_{Me_4Si}^{CDCl_3}$: acetoxyl group: 1.94~2.33 (24 H); aglycon: H-3: 2.72~3.00 (2H,

multiplet); H-2: 5.50 (1H, multiplet); H-6: 6.22 (doublet, $J=2$ Hz); H-8: 6.45 (doublet, $J=2$ Hz); H-3', H-5': 7.04 (doublet, $J=2$ Hz); H-2', H-6': 7.37 (doublet, $J=8$ Hz); sugar protons: quinovosyl methyl group: 1.21 (3H, triplet, $J=6$ Hz); 4.03~4.24 (5H); 4.68~5.32 (7H).

4) *Naringenin-7-[\beta-L-quinovopyranosyl-(1\rightarrow2)-\beta-D-galactopyranoside] (VI)*

Coupling of naringenin (2.4 g) with XI yielded 1.29 g (19.3%) of VI as colorless needles, mp 195~200°C. No taste. $[\alpha]_D^{16} -48.6^\circ$. TLC 0.59. *Anal.* Found: C, 50.18; H, 5.47; Calcd. for $C_{27}H_{32}O_{14} \cdot 4H_2O$: C, 49.69; H, 6.13%. UV λ_{max}^{MeOH} nm (ϵ): 224 (22900), 282 (14500), 328 (2800); $\lambda_{max}^{MeOH-NaOH}$ nm (ϵ): 242 (13900), 282 (74600), 320 (4790), 420 (12800); $\lambda_{max}^{MeOH-AlCl_3}$ nm (ϵ): 310 (27100), 369 (7220); $\lambda_{max}^{MeOH-AlCl_3-HCl}$ nm (ϵ): 308 (23400), 370 (6900); $\lambda_{max}^{MeOH-AcONa}$ nm (ϵ): 281 (26400), 330 (8380). IR ν cm^{-1} : 3340 (OH); 1640 (C=O). Acetate (VI'), mp 226°C. *Anal.* Found: C, 56.04; H, 5.24; Calcd. for $C_{48}H_{48}O_{22} \cdot H_2O$: C, 56.33; H, 5.24%. $[\alpha]_D^{15} -25.0^\circ$ ($c=1.0$, C_6H_5N). NMR $\delta_{Me_4Si}^{CDCl_3}$: acetoxyl group: 1.63~2.12 (18H); 2.30~2.35 (6H, C-4', C-5 acetoxyls); aglycon: H-3: 2.80~3.02 (2H, multiplet); H-2: 5.46 (1H, multiplet); H-6: 6.35 (doublet, $J=3$ Hz); H-8: 6.54 (doublet, $J=2$ Hz); H-3', H-5': 7.14 (2H, doublet, $J=4$ Hz); H-2', H-6': 7.40 (doublet, $J=8$ Hz); sugar protons: quinovosyl methyl group: 1.23 (3H, triplet, $J=6$ Hz); 3.85~4.20 (5H); 4.56~5.43 (7H).

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