Facile Synthesis of the Chalcones and Dihydrochalcones from Naringin, Neohesperidin and Hesperidin

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Dihydrochalcones, Sweeteners, Flavanone Glycosides, UV Spectra, Hydrogenation

The flavanone glycosides naringin, neohesperidin and hesperidin were converted chemically to the corresponding chalcones and dihydrochalcones; the one-step synthesis, performed at room temperature, required the presence of 25% KOH in the reaction mixture for the former and 10% KOH, a catalyst and molecular hydrogen at atmospheric pressure for the latter.

Results and Discussion

The ban of cyclamate from the U.S. market of artificial sweeteners in 1969 was followed by a dramatically increased effort to search for new natural and artificial noncaloric sweeteners. Naringin dihydrochalcone (7) and neohesperidin dihydrochalcone (8) derived from the naturally occurring flavanone glycosides naringin (1) and neohesperidin (2) are intensely sweet tasting compounds, and have a strong potential to serve as a substitute for sucrose, whereas hesperidin dihydrochalcone (9) obtained from the flavanone glycoside hesperidin (3) has no sweet taste1.

The chemical synthesis of 7, 8, and 9 from their corresponding flavanone glycosides is not very economical, since either a two-step synthesis, isolation of the corresponding chalcones (4, 5, and 6) followed by hydrogenation2, or a more complicated hydrogenation procedure, utilizing high pressure is required3.

During preliminary studies on this subject4 we found a facile chemical synthesis using mild conditions that yielded the chalcones as well as the dihydrochalcones from the corresponding flavanone glycosides; depending on the alkalinity of the reaction mixture and the reaction conditions, the flavanone glycosides (Fig. 1) can be converted either in a single step after A (25% KOH) to the corresponding chalcones or in a single step after B (10% KOH, H2, catalyst) to the corresponding dihydrochalcones. The synthesis of the sweet tasting dihydrochalcones proceeds without any complications, and the yields are nearly theoretical. Therefore, the economic character of this novel synthesis is evident. In addition, this synthesis has the advantage over the other known methods5 that there is no pressure required for the hydrogenation

![Synthesis of chalcones and dihydrochalcones from the flavanone glycosides.](image)

1: \( R = \beta\text{-neohesperidosyl}, R_3 = \text{OH}, R_4 = H \),
2: \( R = \beta\text{-neohesperidosyl}, R_1 = \text{OH}, R_2 = \text{OCH}_3, R_3 = \text{OH} \),
3: \( R = \beta\text{-rutinosyl}, R_1 = \text{OCH}_3, R_2 = \text{OH} \),
4: chalcone of 1,
5: chalcone of 2,
6: chalcone of 3,
7: dihydrochalcone of 1,
8: dihydrochalcone of 2,
9: dihydrochalcone of 3.

Fig. 1. Synthesis of chalcones and dihydrochalcones from the flavanone glycosides.
procedure, utilizing a reusable catalyst. The purity of all compounds was secured by thin-layer chromatography. The melting points and UV maxima of the described compounds 1 to 9 are summarized in Table I.

Experimental Section

UV spectra: UV maxima were obtained from the UV spectra as determined in a Cary 14 Recording Spectrophotometer (Table I). The measurements were carried out in 1.0 cm quartz cuvettes containing a solution of 1.0 mg compound/100 ml methanol.

Table I. Melting points (°C) and UV maxima (nm/log ε) of some flavanone glycosides, their chalcones and dihydrochalcones.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p.</th>
<th>λ_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naringin</td>
<td>170-171</td>
<td>283/4.20</td>
</tr>
<tr>
<td>Neohesperidin</td>
<td>239-240</td>
<td>283/4.27</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>261-262</td>
<td>284/4.21</td>
</tr>
<tr>
<td>Naringin chalcone</td>
<td>201-202</td>
<td>364/4.48</td>
</tr>
<tr>
<td>Neohesperidin chalcone</td>
<td>232-233</td>
<td>369/4.19</td>
</tr>
<tr>
<td>Hesperidin chalcone</td>
<td>204-205</td>
<td>368/4.07</td>
</tr>
<tr>
<td>Naringin dihydrochalcone</td>
<td>169-170</td>
<td>281/4.26</td>
</tr>
<tr>
<td>Neohesperidin dihydrochalcone</td>
<td>152-153</td>
<td>282/4.25</td>
</tr>
<tr>
<td>Hesperidin dihydrochalcone</td>
<td>194-195</td>
<td>282/4.19</td>
</tr>
</tbody>
</table>

Melting points: m.p. were determined in a Thiele apparatus and are not corrected (Table I). The chalcones and dihydrochalcones start to soften far below their m.p.

Thin-layer chromatography: TLC was performed on silica gel plates (Merck, 60F-254, 0.25 mm) developed with H₂O-saturated n-butanol; the compounds were visualized under UV light (257 nm)^2.

Naringin (1): The commercially available product (Sigma, Grade 2) was recrystallized from boiling water.

a) Naringin chalcone (4): 1 g of 1, dissolved in 20 ml KOH (25%), was magnetically stirred at room temperature for 2 hours. The yellow-orange reaction mixture was diluted with water to 100 ml and passed through an Amberlite 200 (Rohm & Haas, Philadelphia, Pa.) column (25 × 200 mm). The neutral yellow eluate (125 ml) was collected and placed over night in a refrigerator. The crystallized yellow substance was collected with the aid of a Buchner funnel, washed twice with ice cold water and finally dried in a desiccator. Yield: 640 mg of 4.

b) Naringin dihydrochalcone (7): To 5 g of 1, dissolved in 25 ml KOH (10%), 500 mg palladium black were added. The reaction vessel was flushed with H₂ and finally connected to a small gasometer containing H₂. The orange-yellow reaction mixture was stirred magnetically at room temperature and atmospheric pressure. After 6 hours the catalyst was removed from the reaction mixture with the aid of a Buchner funnel; the resulting clear and colorless filtrate was acidified with 8 ml of conc. HCl and then placed in a refrigerator. After several hours the whitish precipitate was collected with the aid of a Buchner funnel, recrystallized from hot water, washed with ice cold water and finally dried in a desiccator.

Yield: 4.9 g of 7.

Neohesperidin (2): A crude sample obtained from R. E. Leitz (Nutrilite Products, Inc., Lakeview, Ca.) was recrystallized from boiling water.

1) Neohesperidin chalcone (5): 1 g of 2, dissolved in 20 ml KOH (25%), was treated as described for 4. Since 5 did not crystallize in the cold, the column eluate was evaporated to dryness in a rotary vacuum evaporator at 40 °C; yield of the red-orange compound was 875 mg. Crude 5 (100 mg) was dissolved in 5 ml H₂O-saturated n-butanol and placed on top of a silica gel (Woelm, particle size <0.03 mm) column (25 × 160 mm) equilibrated with H₂O-saturated n-butanol. The column was eluted with H₂O-saturated n-butanol under pressure (4 atm.); the first yellow eluate was collected (30 ml) and evaporated to dryness in a rotary vacuum evaporator.

Yield: 80 mg of 5.

b) Neohesperidin dihydrochalcone (8): 5 g of 2, dissolved in 25 ml KOH (10%), were treated as described for 7, and the resulting whitish substance was recrystallized from hot water.

Yield: 4.7 g of 8.

Hesperidin (3): The commercially available product (Sigma, Grade 1) was recrystallized from boiling water.

a) Hesperidin chalcone (6): 1 g of 3, dissolved in 20 ml KOH (25%), was treated as described for 4. Since 6 did not crystallize in the cold, the column eluate was evaporated to dryness in a rotary vacuum evaporator. Yield of the crude red-brown, resin-like material was 660 mg. 100 mg of crude 6 were dissolved in 8 ml of H₂O-saturated n-butanol and placed on top of a DEAE-cellulose (Serva) column (25 × 200 mm) equilibrated with H₂O-saturated n-butanol. The column was eluted with H₂O-saturated n-butanol; the first yellow eluate was collected (100 ml) and evaporated to dryness in a rotary vacuum evaporator.

Yield: 86 mg of 6.
b) Hesperidin dihydrochalcone (9): To 1 g of 3, dissolved in 5 ml KOH (10%), 100 mg palladium black were added and the reaction vessel flushed with H₂ at atmospheric pressure and finally connected to a small gasometer containing H₂. The dark reaction mixture was stirred magnetically at room temperature and after 6 hours the obtained product was diluted with water to 50 ml, the catalyst removed with the aid of a Buchner funnel, and the resulting amber solution was passed through an Amberlite 200 (Rohm & Haas, Philadelphia, Pa.) column (25 x 180 mm). The column was flushed with a total of 300 ml water. The neutral eluate was evaporated to dryness in a rotary vacuum evaporator and yielded 50 mg of a crude resinous amber compound. 100 mg of crude 9 were dissolved in 5 ml of H₂O-saturated n-butanol and the supernatant placed on top of a DEAE-cellulose (Serva) column (25 x 200 mm) equilibrated with H₂O-saturated n-butanol. The column was eluted with H₂O-saturated n-butanol, and the first yellow-amber eluate was collected (100 ml) and evaporated to dryness in a rotary vacuum evaporator.

Yield: 45 mg yellow-amber crystals of 9.

Anal. for C_{28}H_{36}O_{15}·2\frac{1}{2}H_{2}O
Calcd C 51.14 H 6.28,
Found C 50.90 H 5.84.

We thank Mr. R. E. Leitz (Nutrilite Products, Inc., Lakeview, Ca.) for the generous sample of neohesperidin, and we are grateful to Dr. C. P. Schaffner for use of the Cary 14 Recording Spectrophotometer and to Dr. W. Mechlinski for his valuable suggestions concerning HPLC. We appreciate the careful preparation of the manuscript by Ms. Sherry Johanas. This work was supported in part by the National Science Foundation (grant number GI 34287 C). Paper of the Journal Series, New Jersey Agricultural Experiment Station, Rutgers University – The State University of New Jersey, New Brunswick, N. J. 08903. C,H-determinations were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.