

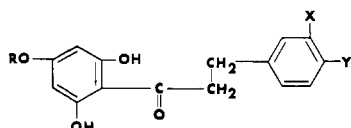
## Dihydrochalcones. Synthesis of Potential Sweetening Agents

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The synthesis of three new, sweet dihydrochalcones and related compounds is reported. One of these, 2',4',6',3-tetrahydroxy-4-n-propoxydihydrochalcone 4'- $\beta$ -neohesperidoside, was found to be approximately 2000 times sweeter than sucrose on a weight basis. Highly specific reaction conditions

were required for various benzaldehydes undergoing Claisen-Schmidt condensations with phloracetophenone 4'- $\beta$ -neohesperidoside. Neohesperidin chalcone and homologous compounds were prepared in 1 to 5 minutes.

The dihydrochalcones of the naturally occurring flavanones, prunin (I), naringin (II), and neohesperidin (III), were reported by Horowitz and Gentili (1963a) to be intensely sweet. On a molar basis, these compounds were reported to be 0.4, 1, and 20 times as sweet as saccharin, respectively. These three dihydrochalcones are similar, and are readily made from the corresponding flavanones.



I (R =  $\beta$ -D-glucosyl, X = H, Y = OH)

II (R =  $\beta$ -neohesperidosyl, X = H, Y = OH)

III (R =  $\beta$ -neohesperidosyl, X = OH, Y = OCH<sub>3</sub>)

Neohesperidose = 2-O- $\alpha$ -L-rhamnopyranosyl-D-glucopyranose

Naringin (IV) (Horowitz, 1964b) is the chief flavonoid constituent of grapefruit, and is available commercially in large quantities. Neohesperidin (V) (Horowitz, 1964b) is found in the unripe fruit of certain varieties of the Seville orange, while prunin (VI) (Hergert, 1962) is a constituent of *Prunus* wood. Neither of the latter two is available commercially at the present time.

The objective of this investigation was to convert IV to other phenolic glycosides, primarily for evaluation as sweetening agents. Compound IV was converted to III and V in large quantities, and three new, sweet dihydrochalcones were synthesized.

Syntheses and conversions of this type have been reported by other workers. For example, Zemplin and coworkers (1942, a and b) have reported the synthesis of the flavanone sakuranin by cyclization of the chalcone obtained from the condensation of 4-methylphloracetophenone-2-glucoside and *p*-hydroxybenzaldehyde. Reduction of this chalcone yielded the dihydrochalcone, asebotin.

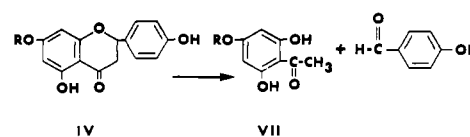
In a similar manner, Hörhammer *et al.* (1966) have synthesized eriodictoyl-5,7-diglucoside from phloracetophenone-2,4-octaacetyl-di- $\beta$ -D-glucoside and protocatechu-aldehyde.

Horowitz and Gentili (1963b) reported that alkaline degradation of IV and V yields a common compound, phloracetophenone-4'- $\beta$ -neohesperidoside (VII). Horowitz (1964b) has an unpublished synthesis of the flavanone pinocembrin 7- $\beta$ -neohesperidoside by cyclization of the chalcone obtained from the condensation of VII and benzaldehyde.

Recently, Kamiya *et al.* (1967) reported the synthesis of naringin and neohesperidin. The chalcones which they cyclized were prepared by the condensation of VII with the appropriate benzaldehyde for 24 and 48 hours. They, too, observed that the reactivity of VII with benzaldehydes was very dependent upon the benzaldehyde employed, to the extent that isomeric benzaldehydes failed to yield the desired chalcone under their reaction conditions. These workers attempted to condense VII with 15 different benzaldehydes, and were successful only with *p*-hydroxybenzaldehyde and isovanillin.

In a recent communication, Chopin and Dellamonica (1966) describe the synthesis of several flavanone 7- $\beta$ -neohesperidosides, including pinocembrin 7- $\beta$ -neohesperidoside and neohesperidin. These compounds were also prepared by cyclization of the chalcone obtained from the condensation of VII with the appropriate benzaldehyde. Under the reaction conditions employed by Chopin and Dellamonica, 12% alkali and 3 days' reaction time, pinocembrin 7- $\beta$ -neohesperidoside and neohesperidin were obtained in 22 and 7% yield, respectively.

The basic starting material for the present synthesis was VII. This compound was readily made by the alkaline degradation of IV.



R =  $\beta$ -neohesperidosyl

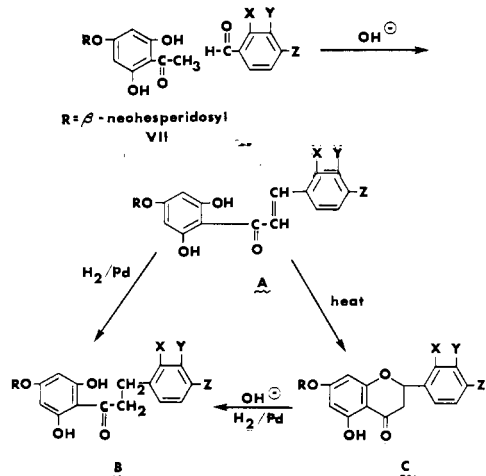
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The degradation and isolation procedure employed was essentially that described by Horowitz and Gentili (1963b). No free rhamnose was detected by paper chromatography after acidification of the reaction mixture with either

dilute hydrochloric acid or dilute sulfuric acid. The acidic cleavage of the neohesperidosyl moiety has been reported by Fox *et al.* (1953) and Seikel (1955). These authors have shown the deliberate partial hydrolysis of IV in dilute acid yields rhamnose and naringenin 7- $\beta$ -D-glucoside or prunin.

The alkaline condensation of VII with the appropriate benzaldehyde yielded a series of chalcones, A. These chalcones were either hydrogenated to the dihydrochalcones (DHC), B, or cyclized to the corresponding flavanones, C, which were, in turn, converted to their respective dihydrochalcones. The flavanones prepared in this investigation are summarized in Table I.



Most chalcone syntheses require several hours or days. Even then, the yields are often poor. The authors obtained neohesperidin chalcone (XII) in >50% yield in a reaction time of approximately 1 minute. The reaction conditions necessary for such rapid chalcone formation were remarkably specific for each aldehyde. Neohesperidin chalcone was obtained in 70 to 80% of theoretical yield, based on VII, when VII was condensed with isovanillin at 75° to 100°C. for a period of time ranging from 13 to 2 minutes, respectively. The optimum temperature and time were about 100°C. for 3 to 5 minutes. Little or no homoneohesperidin chalcone (XIII) or 2',4',6',3-tetrahydroxy-4-*n*-propoxychalcone 4'- $\beta$ -neohesperidoside (XIV) was obtained when either 4-ethoxy or *n*-propoxy

3-hydroxybenzaldehyde was substituted for isovanillin under these conditions. Moderate yields of XIII and XIV were obtained when the reaction temperature was raised to 115–120°C. and the alkali concentration decreased.

The yields of XII were calculated from isolated V and the amount lost in isolation and purification. The amount of V lost was estimated by paper chromatographic analysis of the filtrates. For our purposes, it was assumed that XII cyclized quantitatively to V.

The DHC's obtained by catalytic reduction of the crude chalcones invariably contain varying amounts of unreacted VII, aldehyde, and other impurities. It was frequently difficult or impossible to obtain pure DHC by this route. The preparation of the pure DHC's was greatly simplified by cyclization of the chalcone to the flavanone and the subsequent reduction in alkali of the purified flavanone. The purification of the 3-hydroxy-4-alkoxy flavanones was greatly simplified by their comparative insolubility in hot water, while VII was fairly soluble (>10 grams per liter at 65°C.). The unreacted VII was completely removed from these flavanones by filtration at an elevated temperature.

The taste qualities and formulations of the dihydrochalcones and an attempt to correlate structure with activity have been discussed by Inglett *et al.* (1967). The sweetness values of the new dihydrochalcones and closely related analogs are summarized in Table II, expressed in sucrose equivalents on a weight basis.

These sweet dihydrochalcones have a characteristic cooling sensation, frequently described as a menthol-type aftertaste. Efforts to synthesize a sweet dihydrochalcone without this taste sensation were not successful.

## EXPERIMENTAL

**Phloracetophenone 4'- $\beta$ -Neohesperidoside (VII).** Five hundred grams (0.77 mole) of naringin hydrate were added to a solution of 500 grams (7.7 moles) of potassium hydroxide pellets and 4000 ml. of water. The mixture was stirred at room temperature for 1 $\frac{1}{4}$  hours, then refluxed for 1 $\frac{1}{4}$  hours. The cold solution was diluted with approximately 2000 grams of ice prior to acidification to pH 6 with cold 6*N* hydrochloric acid. The product was collected by filtration.

The crude product was recrystallized from water to yield 292 grams (70%) of air-dried phloracetophenone 4'- $\beta$ -neohesperidoside hydrate, m.p. 155–60°C. (Horowitz and Gentili, 1963b; m.p. 164–66°C.).  $R_f$  value, 0.85.

**Naringin (IV).** Eight grams (0.016 mole) of phloracetophenone 4'- $\beta$ -neohesperidoside and 8 grams (0.065 mole) of *p*-hydroxybenzaldehyde followed by 20 ml. of 95% ethyl alcohol were added to a solution of 100 grams of potassium hydroxide pellets and 70 ml. of water. The mixture was refluxed for  $\frac{1}{2}$  hour. The cold solution was poured onto 400 grams of ice, acidified to pH 5.8 at 5° to 10°C. with cold, dilute hydrochloric acid, and stirred at 0° to 5°C. for approximately 1 hour. The naringin chalcone which separated was collected,  $\lambda_{\text{max}}^{\text{EtOH}}$  363 m $\mu$ . The chalcone was heated to 90° to 100°C. in 75 ml. of water for  $\frac{1}{2}$  hour, and the product collected from the cold solution. The crude naringin was treated with charcoal and recrystallized from 60 ml. of water to yield 3.6 grams (35%) of naringin dihydrate, m.p. 165–68° (Asahina and Inubuse, 1928; m.p. 171°C.).  $R_f$  value, 0.68.

Table I. Flavanones

Number	Compound	Substituted		
		X	Y	Z
VIII	2',5,7-Trihydroxy-flavanone 7- $\beta$ -neohesperidoside	OH	H	H
IX	3',5,7-Trihydroxy-flavanone 7- $\beta$ -neohesperidoside	H	OH	H
IV	Naringin	H	H	OH
V	Neohesperidin	H	OH	OCH <sub>3</sub>
X	Homoneohesperidin	H	OH	OCH <sub>2</sub> CH <sub>3</sub>
XI	3',5,7-Trihydroxy-4'- <i>n</i> -propoxy-flavanone 7- $\beta$ -neohesperidoside	H	OH	OCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>

Table II. Dihydrochalcone Sweetness Values

Compound	Substitute			Sweetness Value	
	X	Y	Z	Threshold level	5% Sucrose level
XV	OH	H	H	Slightly bitter	
XVI	H	OH	H	~100 × sucrose	~100 × sucrose
II	H	H	OH	~100 × sucrose	~100 × sucrose
III	H	OH	OCH <sub>3</sub>	~1000 × sucrose	~1000 × sucrose
XVII	H	OH	OCH <sub>2</sub> CH <sub>3</sub>	~1000 × sucrose	~1000 × sucrose
XVIII	H	OH	OCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	~2000 × sucrose	~2000 × sucrose

**2',5,7-Trihydroxyflavanone 7-β-Neohesperidoside (VIII).** Eighteen grams (0.038 mole) of phloracetophenone 4'-β-neohesperidoside and 10 ml. (0.1 mole) of salicylaldehyde were added to a solution of 200 grams of potassium hydroxide pellets, 300 ml. of water, and 50 ml. of 95% ethanol. The mixture was refluxed for 2 hours, then poured onto 500 grams of ice and acidified to pH 5.5 at <10°C. with cold dilute hydrochloric acid. After 18 hours at 5° to 10°C., the crude 2,2',4',6'-tetrahydroxychalcone 4'-β-neohesperidoside was collected,  $\lambda_{\max}^{\text{EtOH}}$  365 m $\mu$ . The chalcone was heated for 1/2 hour at 90° to 100°C. in 200 ml. of water. The product was removed by filtration at 35°C., dissolved in 200 ml. of hot water, and treated with decolorizing charcoal. The precipitate was collected at 40°C. to yield 3.7 grams (17%) of 2',5,7-trihydroxyflavanone 7-β-neohesperidoside, m.p. 250–52°C. *R<sub>f</sub>* value, 0.71.

Analysis. Calcd. for C<sub>27</sub>H<sub>32</sub>O<sub>14</sub> · 1/2H<sub>2</sub>O: C, 55.01; H, 5.65. Found: C, 54.82; H, 5.76.

**3',5,7-Trihydroxyflavanone 7-β-Neohesperidoside (IX).** Six grams (0.05 mole) of 3-hydroxybenzaldehyde and 14.5 grams (0.033 mole) of phloracetophenone 4'-β-neohesperidoside were added to 400 ml. of 10% potassium hydroxide solution; the mixture was refluxed for 2 hours. The solution was poured onto 400 grams of ice and acidified to pH 5 at 5° to 10°C. with cold dilute hydrochloric acid. After several hours at 0° to 5°C., the 3,2',4',6'-tetrahydroxychalcone 4'-β-neohesperidoside was collected,  $\lambda_{\max}^{\text{EtOH}}$  335 m $\mu$ . The chalcone was purified by dissolving it in 600 ml. of 4% potassium hydroxide and reacidifying it to pH 5 at 5° to 10°C. The 3,2',4',6'-tetrahydroxychalcone 4'-β-neohesperidoside was heated to 100°C. in 250 ml. of water for 1/2 hour. After 18 hours at 5° to 10°C., the precipitated product was collected, and recrystallized from water to yield 8 grams (45%) of 3',5,7-trihydroxyflavanone 7-β-neohesperidoside, m.p. 162–65°C. *R<sub>f</sub>* value, 0.68.

Analysis. Calcd. for C<sub>27</sub>H<sub>32</sub>O<sub>14</sub> · 1/2H<sub>2</sub>O: C, 55.01; H, 5.65. Found: C, 54.92; H, 5.69.

**Neohesperidin (V).** METHOD A. A solution of 50 grams of potassium hydroxide pellets and 50 ml. of water was heated to 100°C. Twenty-four grams (0.05 mole) of phloracetophenone 4'-β-neohesperidoside were added and the mixture was stirred at this temperature until a clear red solution was attained, usually 3 minutes. Twelve grams (0.08 mole) of isovanillin were added to the hot solution which was stirred at 100°C. for 5 minutes. The reaction mixture was poured onto 300 grams of crushed ice, and acidified to pH 5.7 at 5° to 10°C. with cold, dilute hydrochloric acid. After 18 hours at 0° to 5°C., the neohesperidin chalcone, VIII, was collected,  $\lambda_{\max}^{\text{EtOH}}$  370 m $\mu$ . The chalcone was heated to 80–90°C. in 300 ml. of water for 1/2

hour, and the precipitate collected at 40°C. The crude neohesperidin was triturated with 200 ml. of water at 65°C. and filtered at this temperature to yield 15.7 grams (51%) of neohesperidin free of any phloracetophenone 4'-β-neohesperidoside, m.p. 238–40°C. An analytical sample was recrystallized from water, m.p. 239–40°C. *R<sub>f</sub>* value, 0.67 (Zemplin and Tettamanti, 1938; Karrer, 1949; m.p. 239–40°C.)

Analysis. Calcd. for C<sub>28</sub>H<sub>34</sub>O<sub>15</sub>: C, 55.09; H, 5.61. Found: C, 55.23; H, 5.57.

METHOD B. An identical condensation mixture was poured into 200 ml. of water instead of ice. The solution was acidified to pH 5.8 at 75° to 85°C. with dilute hydrochloric acid, and the precipitate collected at 25°C. The product was purified by trituration with 200 ml. of water at 70°C., and filtered at that temperature to yield 17.8 grams (58%) of neohesperidin, m.p. 238–40°C.

METHOD C. A solution consisting of 5 grams (0.0078 mole) of naringin hydrate, 8.6 grams (0.15 mole) of potassium hydroxide, and 40 ml. of water was refluxed for 1 hour. To the refluxing solution, an additional 17 grams (0.30 mole) of potassium hydroxide were added, followed by 3 grams (0.02 mole) of isovanillin. The mixture was refluxed for 5 minutes, and after the addition of approximately 100 grams of ice, the solution was acidified to pH 6 at <10°C. with cold, dilute hydrochloric acid. Crude neohesperidin chalcone was collected after 18 hours at 0° to 5°C. The chalcone was heated to 80° to 90°C. in 125 ml. of water for 1/2 hour. Filtration of the cold solution yielded 1.5 grams (32%) of neohesperidin, m.p. 235–40°C.

**3',5,7-Trihydroxy-4'-ethoxyflavanone 7-β-Neohesperidoside (Homoneohesperidin) (X).** METHOD A. A solution of 24 grams of potassium hydroxide pellets and 40 ml. of water was heated to 115°C. Fifteen grams (0.031 mole) of phloracetophenone 4'-β-neohesperidoside were added to the hot solution. A clear, red solution resulted approximately 1/2 minute after this addition. To this hot, clear solution, 7.5 grams (0.045 mole) of 4-ethoxy-3-hydroxybenzaldehyde, prepared by the method of Beke and Szóntay (1958), were added. The mixture was maintained at 115° to 120°C. for 3 minutes, and then poured onto 300 grams of ice. The resulting solution was acidified to pH 5.8 with cold dilute hydrochloric acid at <10°C. The solution was stirred in an ice bath for 1 1/2 hours, and the precipitate removed by filtration. The homoneohesperidin chalcone, IX, was cyclized to homoneohesperidin by heating the filtrate to 80° to 90°C. for 1/2 hour. The crude homoneohesperidin was removed after 2 days at room temperature, and was recrystallized twice from 125 ml. of water and once from 300 ml. of water to yield 2.6 grams (13%) of

homoneohesperidin, m.p. 228–30°C.  $R_f$  value, 0.60.

Analysis. Calcd. for  $C_{29}H_{36}O_{15}$ : C, 55.73; H, 5.81. Found: C, 55.63; H, 5.84.

**METHOD B.** A solution of 12 grams of potassium hydroxide pellets, 5 ml. of water, and 25 ml. of 95% ethanol was cooled to 25°C. Two grams (0.0042 mole) of phloracetophenone 4'- $\beta$ -neohesperidoside and 1 gram (0.006 mole) of 4-ethoxy-3-hydroxybenzaldehyde were added to the solution. The mixture was stirred rapidly at room temperature for 4½ days, then poured onto 200 grams of ice and acidified to pH 5.8 with cold dilute hydrochloric acid. After a week at 5° to 10°C., the homoneohesperidin chalcone was collected,  $\lambda_{max}^{ETOH}$  370 m $\mu$ . The chalcone was heated to 80° to 90°C. for ½ hour in 100 ml. of water, and the crude homoneohesperidin was collected by filtration and recrystallized from 30 ml. of water to yield 0.25 gram (10%) of homoneohesperidin, m.p. 226–29°C.

**3',5,7-Trihydroxy-4'-*n*-propoxyflavanone 7- $\beta$ -Neohesperidoside (XI).** A solution of 12 grams of potassium hydroxide pellets and 20 ml. of water was heated to 110° to 115°C. Seven and one-half grams (0.016 mole) of phloracetophenone 4'- $\beta$ -neohesperidoside were added to the solution. To the resulting hot, clear solution, 3.75 grams (0.022 mole) of 3-hydroxy-4-*n*-propoxybenzaldehyde, prepared by the method of Beke and Szóntay (1958), were added. The solution was maintained at 115° to 120°C. for 5 minutes, then poured onto 150 grams of ice. The solution was acidified to pH 6.5 at <10°C. with cold, dilute hydrochloric acid. This solution had an intense chalcone absorption at 370 m $\mu$ . Cyclization of the chalcone to the flavanone was effected by heating the solution to 80° to 90°C. for ½ hour. The cold mixture was extracted with two 100-ml. portions of methylene chloride, from which 1.5 grams of unreacted 3-hydroxy-4-*n*-propoxybenzaldehyde were obtained. The precipitate was collected from the

cold aqueous phase, and the crude product was recrystallized twice from 100 ml. of water and filtered at 30°C., then triturated twice with 35 ml. of water, and filtered at 80°C. to yield 1.3 grams (13%) of 3',5,7-trihydroxy-4'-*n*-propoxyflavanone 7- $\beta$ -neohesperidoside, m.p. 222–24°C.  $R_f$  value, 0.52.

Analysis. Calcd. for  $C_{30}H_{38}O_{15}$ : C, 56.42; H, 5.99. Found: C, 56.13; H, 6.40.

The dihydrochalcones were prepared by reduction of the isolated chalcones or by reduction of the flavanones under alkaline conditions. Typical examples of each are:

**Neohesperidin Dihydrochalcone (III).** **METHOD A** (Horowitz, 1964a). A solution of 200 grams of neohesperidin in 1600 grams of 8.5% potassium hydroxide solution was hydrogenated on a Parr shaker for 3 hours at an initial pressure of 50 p.s.i.g. in the presence of 20 grams of 10% palladium on charcoal. The solution was acidified to pH 6 with cold, dilute hydrochloric acid, the catalyst was removed by filtration, and the precipitate collected from the cold solution and washed with water to yield 232 grams (100%) of air-dried neohesperidin dihydrochalcone hydrate. An analytical sample of neohesperidin dihydrochalcone was prepared by recrystallization from water, m.p. 153–55°C. (Horowitz and Gentili, 1963a, 152–54°C.).  $R_f$  value, 0.43.

Analysis. Calcd. for  $C_{28}H_{36}O_{15}$ : C, 54.91; H, 5.92. Found: Water loss on drying, 14.85%; C, 55.02; H, 5.94.

**METHOD B.** The neohesperidin chalcone, prepared from the condensation of 475 grams (1 mole) of phloracetophenone 4'- $\beta$ -neohesperidoside and 240 grams (1.575 moles) of isovanillin, was collected at pH 6.7. The crude, wet product was washed with 15 liters of water. A solution of 215 grams of potassium hydroxide in 235 ml. of water was added with stirring to the wet cake to give 4 liters of solution which was hydrogenated on a Parr shaker at an

Table III. Dihydrochalcones

Compound	Alkali Concentration, %	M.P., ° C.	$R_f$	Yield, %	Empirical Formula	Analysis			
						Calculated		Found	
						C	H	C	H
Naringin dihydrochalcone (II)	10	169–70 <sup>a</sup>	0.45	90+					
2,2',4',6'-Tetrahydroxydihydrochalcone 4'- $\beta$ -neohesperidoside (XV)	20	144–45 (soften 140)	0.58	80	$C_{27}H_{34}O_{14} \cdot \frac{1}{2}H_2O^b$	54.83	5.96	54.91	5.86
2',4',6',3-Tetrahydroxydihydrochalcone 4'- $\beta$ -neohesperidoside (XVI)	10	159–61 (soften 155)	0.54	72	$C_{27}H_{34}O_{14}$	55.67	5.88	55.37	5.88
Homoneohesperidin dihydrochalcone (XVII)	20	142–45	0.43	74	$C_{29}H_{36}O_{15}$	55.55	6.11	55.14	6.03
2',4',6',3-Tetrahydroxy-4- <i>n</i> -propoxydihydrochalcone 4'- $\beta$ -neohesperidoside (XVIII)	20	142–44 (soften 140)	0.37	50	$C_{30}H_{40}O_{15}$ $C_{30}H_{40}O_{15} \cdot \frac{1}{2}H_2O^b$	56.21 55.43	6.29 6.36	55.70	6.49

<sup>a</sup> Horowitz and Gentili (1963a); Jorio (1959), m.p. 168–69°C., 164°C., respectively.

<sup>b</sup> Analysts commented on extremely hygroscopic nature of many of these samples.

initial pressure of 50 p.s.i.g. in the presence of 50 grams of 5% palladium or charcoal. The solution was neutralized to pH 9 with cold 33% sulfuric acid at <math>10^{\circ}\text{C}</math>, the catalyst removed by filtration, and the filtrate acidified to pH 6.5. After 18 hours at  $0^{\circ}$  to  $5^{\circ}\text{C}</math>, the precipitate was collected. The product was recrystallized from 3.5 liters of water to yield 356 grams of air-dried material. A second recrystallization from 15 liters of water yielded 340 grams (47%) of neohesperidin dihydrochalcone hydrate, m.p. 153–55°C.$

The reduction of large quantities of chalcone in alcohol was accompanied by appreciable cyclization to the corresponding flavanone. This was avoided by the use of alkaline solutions

Because of the ease of purification, Method A was the method of choice. Ultimately, all the dihydrochalcones were prepared this way. The remaining dihydrochalcones are summarized in Table III.

All melting points are uncorrected. The paper chromatography was done with Whatman No. 3 filter paper. The chromatograms were developed in a 1% hydrochloric acid medium. The developed chromatogram was irradiated with ultraviolet light or sprayed with 2,6-dichloro-1,4-quinone-4-chlorimide indicator.

**Sweetness Evaluation.** The sweetness values of the dihydrochalcones were determined by panel evaluation with a minimum of five people per panel. In a typical comparison test, a 0.0045% solution of III was judged by several panels to be about equal to a 5% sucrose solution, while a 0.0045% solution of XVII was rated as being between a 4 and a 5% sucrose solution. Based on these results, III and XVII would have sweetness values in the range of 1000 to 1200 and 900 to 1100 times sucrose, respectively.

In a single test comparing II and III with saccharin on a molar basis, the authors' conclusions regarding this relative sweetness were in general agreement with those reported by Horowitz and Gentili (1963a).

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