[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Flavanones and Related Compounds. I. The Preparation of Polyhydroxychalcones and -Flavanones

BY T. A. GEISSMAN AND R. O. CLINTON[1]

A number of polyhydroxychalcones and -flavanones have been prepared for a spectrographic study of certain reduction products of the flavanones.[1a]

Most of the compounds prepared in the present study are not new and are mentioned only in those cases in which some revision of their properties appears to be necessary. Eight new chalcones and ten new flavanones are described, as well as acyl derivatives of all of these.

Chalcones.—A considerable variety of methods are available for the preparation of polyhydroxychalcones. Although possessing certain limitations, the most generally suitable methods involve the condensation of a suitably substituted acetophenone and the appropriate benzaldehyde by means of alkali. Most of the compounds described here were prepared by this general procedure. The use of Russell's[2] method was found necessary in a few cases.

The preparation of certain chalcones containing the 2'-hydroxy-4',6'-dimethoxy nucleus can be accomplished conveniently by the methylation of flavanones containing the 5,7-dihydroxy nucleus. Readily available substances of this class are naringenin, hesperidin and homoeriodictyol. The methylation procedure used must be carefully selected. Taking naringenin as an example, the use of diazomethane results in the methylation only of the hydroxyl groups in the 4' and 7 positions; the use of dimethyl sulfate and alkali can be controlled to yield a mixture of the 4'-methyl ether and the 4',7-dimethyl ether; or when carried out vigorously, the 2',4',6',4-tetramethoxychalcone accompanied by varying amounts of 2',4',4-trimethoxy-6'-hydroxychalcone.

Satisfactory yields of the chalcone trimethyl ether along with some of the tetramethyl ether, can be obtained by the methylation of naringenin or naringenin-4',7-dimethyl ether by means of methyl *p*-toluenesulfonate and potassium carbonate in a dry solvent. With care, some naringenin trimethyl ether can be isolated from the reaction mixture, indicating that methylation of the 5-hydroxyl group of the flavanone occurs. It has been found best to treat the reaction mixture with alkali and thus to open any flavanone trimethyl ether to the chalcone, and then to effect a separation of the alkali-insoluble chalcone tetramethyl ether.

Flavanones.—The flavanones were in most cases prepared by ring closure of the appropriate chalcones. The acid or base-catalyzed isomerization of a 2'-hydroxychalcone into the corresponding flavanone seldom goes to practical completion, and the difficulties encountered in preparing polyhydroxyflavanones largely involve the separation of the resulting mixture of chalcone and flavanone. Crystallization from solvents such as alcohols, or even ethers and esters which are not dry, frequently results in the formation of additional amounts of chalcone and consequently in the contamination of samples of flavanone already nearly pure.

The direct reduction of a flavone (luteolin) to a flavanone (eriodictyol) has been carried out, and is the first instance of the reduction of a naturally-occurring flavone to a naturally-occurring flavanone.

Experimental[3]

Polyhydroxychalcones

Hot Condensation.—To a solution of equimolar amounts of the aldehyde and ketone in the minimum amount of alcohol was added a 50% solution of potassium hydroxide (2 g. per g. of ketone). When the aldehyde or ketone contains the *o*-dihydroxyl grouping the addition of the alkali is best carried out under nitrogen. The flask was stoppered securely and heated at 50° for fifteen to twenty hours. Ice was added and the mixture acidified with 6 *N*

TABLE I

CHALCONES PREVIOUSLY REPORTED

Chalcone[a]	Melting point, °C. Obs.	Rep.
2',4-Dihydroxy[b]	162.0–162.5	145[e]
Dibenzoate	106.0–106.5	120[e]
2',3',4',4-Tetrahydroxy[c]	225.0–225.5	217[e,f]
Tetrabenzoate	118.0–118.5	105[e]
2',4',4-Trihydroxy[c]	209.5–210.0	202–204[g]
2,2',4'-Trihydroxy[c,d]	193.5–194.0	188[h]
2',4,5'-Trihydroxy[b]	231–232	222–224[i]
Tribenzoate	152.0–152.5	134–136[i]
2',3,4'-Trihydroxy[c]	228–229 dec.	209[j]
Triacetate	100	100[j]
2',3',4'-Trihydroxy	169.5–170.0	165–166[k]
4',4-Dihydroxy	203.5–204.0	197[l]
2,2',3',4'-Tetrahydroxy	232–234 dec.	224–225 dec.[m]

[a] Numbering according to *Chem. Abs.* [b] Hot condensation method. [c] Cold condensation method. [d] When prepared by hot condensation a yellow compound of m. p. 130.5–131.5° was obtained. This was not further characterized. [e] Russell and Todd, *J. Chem. Soc.*, 421 (1937). [f] Private communication from Dr. Alfred Russell. [g] Nadkarni and Wheeler, *J. Chem. Soc.*, 1320 (1938). [h] Goschke and Tambor, *Ber.*, **45**, 186 (1912). [i] Russell and Clark, THIS JOURNAL, **61**, 2651 (1939). [j] Tambor, *Ber.*, **49**, 1706 (1916). [k] Saiyad, Nadkarni and Wheeler, *J. Chem. Soc.*, 1737 (1937); Shinoda, *J. Pharm. Soc. Japan*, **48**, 214 (1928) (*Chem. Abs.*, **22**, 2947 (1928)). [l] Vorländer, *Ber.*, **58**, 128 (1925). [m] Ellison, *J. Chem. Soc.*, 1720 (1927).

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(1a) Geissman and Clinton, THIS JOURNAL, **68**, 700 (1946).

(2) Russell, *J. Chem. Soc.*, 218 (1934); Russell and Todd, *ibid.*, 1066 (1934); 421 (1937).

(3) All melting points are corrected.

TABLE II

NEW CHALCONES

Chalcone	Color[e]	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2,2′-Dihydroxy[a]	br.y.	160–161 dec.	$C_{15}H_{12}O_3$	74.97	5.04	74.78	5.24
Diacetate	c.	95.5–96	$C_{19}H_{16}O_5$	70.36	4.97	70.25	5.13
2′,4-Dihydroxy-4′-methoxy[b]	br.y.	176–177	$C_{16}H_{14}O_4$	71.09	5.22	70.80	5.22
Diacetate	p.y.	103–103.5	$C_{20}H_{18}O_6$	67.79	5.12	67.67	5.22
2,2′,5′-Trihydroxy[c]	br.o.	200–202 dec.	$C_{15}H_{12}O_4$	70.30	4.69	70.06	4.89
Tribenzoate	c.	151–151.5	$C_{36}H_{24}O_7$	76.05	4.26	75.83	4.32
3,4-Dihydroxy[a]	br.y.	204–205 dec.	$C_{15}H_{12}O_3$	74.98	5.00	74.85	5.12
Diacetate	c.	124.5–125	$C_{19}H_{16}O_5$	70.36	4.97	70.17	5.00
2′,3′,4′-Trihydroxy-3,4-dimethoxy[a]	br.o.-y.	143–145	$C_{17}H_{16}O_6$	64.55	5.10	64.36	5.31
Triacetate	p.y.	151–152	$C_{23}H_{22}O_9$	62.44	5.01	62.26	5.03
2′,4′-Dihydroxy-4-ethoxy[b]	l.o.-y.	183.5–184	$C_{17}H_{16}O_4$	71.80	5.67	71.79	5.80
Diacetate	p.y.	90.5–91	$C_{21}H_{20}O_6$	68.47	5.47	68.34	5.57
2′,2,4-Trihydroxy[b]	l.o.	164–165 dec.	$C_{15}H_{12}O_4$	70.30	4.69	70.14	4.81
Triacetate	p.y.	134–134.5	$C_{21}H_{18}O_7$	65.96	4.74	65.86	4.82
2′-Hydroxy-3,4,5,6′-tetrabenzyloxy[f]	l.y.	123–124	$C_{43}H_{36}O_6$	79.61	5.59	79.46	5.63
Acetate	c.	114.5–115	$C_{45}H_{38}O_7$	78.24	5.55	78.23	5.64
2′,4′-Diacetoxy-3,4,5-tris-benzyloxy[f]	p.y.	146.5–147	$C_{40}H_{34}O_8$	74.50	5.32	74.48	5.46

[a] Prepared by the cold condensation method. [b] Preparation described in text. [c] Prepared by the hot condensation method. [d] Russell and Clark, THIS JOURNAL, **61**, 2651 (1939), report, m. p. 137–139°. [e] br., bright; y., yellow; o., orange; p., pale; c., colorless; l., light. [f] *cf.* Clinton and Geissman, THIS JOURNAL, **65**, 85 (1943).

hydrochloric acid (congo red). If the resulting precipitate was crystalline it was dried and crystallized repeatedly from a suitable solvent; if it was oily, it was taken up in ether, washed with saturated sodium bisulfite and finally subjected to steam distillation. The residue could then be crystallized.

Cold Condensation.—To a cold (−5°) suspension of equimolar quantities of the aldehyde and ketone in alcohol (2 ml. per g. of ketone) was added, with shaking, a cold (−5°) 60% solution of potassium hydroxide (14 ml. per g. of ketone). The flask was securely stoppered and allowed to stand at room temperature for about a week, with occasional shaking. The product was isolated as described above. This procedure is substantially that used by Nadkarni and Wheeler[4] but differs in details.

Known Chalcones.—A total of thirty-five chalcones previously recorded in the literature were prepared. Of these, the melting points of nine did not correspond with previously published values. In cases where the discrepancies were considerable our preparations were analyzed. These compounds are listed in Table I.

New Chalcones.—Eight new chalcones were prepared and characterized by means of acyl derivatives. These compounds are listed in Table II. Two of these chalcones were prepared by procedures which differed enough from the general methods described above to warrant their description here.

2′,4-Dihydroxy-4′-methoxychalcone.—The application of the general methods described above to peonol and *p*-hydroxybenzaldehyde gave oily products which could be purified only with great difficulty. The following procedure gave good results.

Five grams of peonol and 2.7 g. of *p*-hydroxybenzaldehyde were dissolved in 75 ml. of boiling alcohol. To this solution at 55° was added 27 ml. of 60% potassium hydroxide solution and the clear solution allowed to stand at room temperature for one week. The mixture set to a mass of long orange needles; it was worked up by acidification in the cold and recrystallization of the product from alcohol. There was obtained 6.7 g. of bright yellow needles, m. p. 176–177°.

2′,4′-Dihydroxy-4-ethoxychalcone.—To a solution of 7.5 g. of resacetophenone and 7.5 g. of *p*-ethoxybenzaldehyde in 50 ml. of hot alcohol was added 40 ml. of 60% potassium hydroxide solution. The deep orange solution was allowed to stand at room temperature for a week. The partially crystalline mixture was poured onto ice and acidified with hydrochloric acid. The crude chalcone was triturated with sodium bicarbonate solution to remove *p*-ethoxybenzoic acid and then recrystallized several times from dilute alcohol, and finally from a benzene–alcohol mixture. The chalcone formed light orange-yellow needles, sintering at 165°, m. p. 183.5–184°.

2′,2,4-Trihydroxychalcone.—This was prepared by the condensation of 2,4-dibenzoyloxybenzaldehyde and 2-benzoyloxyacetophenone by Russell's method,[2] followed by saponification of the resulting 2′,2,4-trisbenzoyloxychalcone.

Flavanones

Acid Isomerization.—To a hot solution of 1 g. of the chalcone in 50–75 ml. of alcohol was added 3% aqueous hydrochloric acid until a permanent turbidity appeared. Enough alcohol was added to give a clear solution and the mixture refluxed for twenty-four hours. On cooling the mixture the unchanged chalcone usually separates. The filtered solution was evaporated and cooled and the crude chalcone–flavanone mixture washed well with water and dried. Separation was effected by crystallization from a solvent selected by tests on a small sample. In general, the following solvents proved the most useful: For highly hydroxylated compounds, isopropyl ether; for methoxylated compounds, carbon bisulfide; for intermediate cases, ethyl acetate–benzene mixtures. In all of these solvents the chalcone is usually the more soluble, the flavanone insoluble or nearly so.

Alkaline Isomerization.—One gram of the chalcone was dissolved in slightly more than the amount of 1% sodium hydroxide solution equivalent to all of the free hydroxyl groups. A few ml. of alcohol was added, the solution was refluxed for one-half hour and allowed to stand overnight. The crude chalcone–flavanone mixture was precipitated by the addition of dilute acetic acid, separated, dried and purified by crystallization from a selected solvent.

Known Flavanones.—A total of twenty-three flavanones previously recorded in the literature were prepared. Two of these had melting points appreciably different from any previously given: 7,3′,4′-trihydroxyflavanone melted at 232–234° (lit.[5] 224–226°) and 3′,7-dihydroxyflavanone melted at 197–198° (lit.[6] 182–183°).

(4) Nadkarni and Wheeler, *J. Chem. Soc.*, 1320 (1938).

(5) Saiyad, Nadkarni and Wheeler, *J. Chem. Soc.*, 1737 (1937).

(6) Tambor, *Ber.*, **49**, 1706 (1916).

TABLE III

NEW FLAVANONES

Flavanone[a]	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
7,8,4′-Trihydroxy	193.5–194	$C_{15}H_{12}O_5$	66.17	4.41	66.23	4.65
Triacetate	165–166	$C_{21}H_{18}O_8$	63.31	4.55	63.35	4.64
4′-Hydroxy	186–187	$C_{15}H_{12}O_3$	74.98	5.00	74.85	5.22
Acetate	158–158.5	$C_{17}H_{14}O_4$	72.33	5.00	72.35	5.11
7-Hydroxy-4′-methoxy	184.5–185	$C_{16}H_{14}O_4$	71.09	5.22	70.95	5.24
Acetate	114–114.5	$C_{18}H_{16}O_5$	69.22	5.17	69.13	5.36
7,8,2′-Trihydroxy	215–216 (dec.)	$C_{15}H_{12}O_5$	66.17	4.41	65.95	4.5
Triacetate	119–119.5	$C_{21}H_{18}O_8$	63.31	4.55	63.45	4.68
7-Hydroxy-4′-ethoxy	212–213 (dec.)	$C_{17}H_{16}O_4$	71.80	5.67	71.71	5.81
Acetate	107.5–108	$C_{19}H_{18}O_5$	69.93	5.58	69.92	5.64
4′,7-Dihydroxy-3′-methoxy	206–207 (dec.)	$C_{16}H_{14}O_5$	67.11	4.93	67.01	5.01
Diacetate	123–123.5	$C_{20}H_{18}O_7$	64.86	4.90	64.69	5.07
7,8-Dihydroxy-3,′4′-dimethoxy	198–199	$C_{17}H_{16}O_6$	64.55	5.10	64.59	5.27
Diacetate	151.5–152	$C_{21}H_{20}O_8$	63.00	5.04	62.90	5.10
7,8,3′,4′-Tetrahydroxy	252–254 (dec.)	$C_{15}H_{12}O_6$	62.50	4.20	62.31	4.32
Tetraacetate	125.5–126.5	$C_{23}H_{20}O_{10}$	60.52	4.42	60.47	4.55
2′-Hydroxy	165–165.5	$C_{15}H_{12}O_3$	74.97	5.04	75.05	5.11
Acetate	148–148.5	$C_{17}H_{14}O_4$	72.33	5.00	72.23	5.14
5,4′-Dihydroxy	215.5–216.5 (dec.)	$C_{15}H_{12}O_4$	70.30	4.69	70.18	4.84
Diacetate	118–118.5	$C_{19}H_{16}O_6$	67.05	4.74	66.92	4.90

[a] All of the compounds, with one exception, form colorless crystals. 7,8,3′,4′-Tetrahydroxyflavanone retained a light tan color which could not be entirely removed.

New Flavanones.—Ten new flavanones have been prepared, all by acid isomerization of the corresponding chalcones. These compounds are listed in Table III. In two cases, where the intermediate chalcone contained a 2-hydroxy group, acid isomerization gave only the corresponding flavylium salt.

2′,4′-Dihydroxyflavylium Chloride.—A mixture of 6.5 g. of 2′,4′,2-trihydroxychalcone, 75 ml. of alcohol, 75 ml. of water and 3 ml. of concentrated hydrochloric acid was refluxed for eight hours. The resulting bright orange-red solution was cooled and filtered, yielding 5.9 g. of an orange-red semi-crystalline precipitate. Extraction of this air-dried precipitate with isopropyl ether effected a separation into chalcone (soluble) and flavylium salt (insoluble). The latter material was precipitated several times from absolute alcohol solution with absolute ether, yielding the flavylium chloride as small deep-red needles, m. p. 151–153° (dec.). The solution in concentrated sulfuric acid exhibited a green fluorescence.

Anal. Calcd. for $C_{15}H_{11}O_3Cl\cdot H_2O$: C, 61.54; H, 4.48; H_2O, 6.16. Found: C, 61.50; H, 4.55; H_2O, 6.09.

2′,7-Dihydroxyflavylium Chloride.—Treatment of 2′,2,4-trihydroxychalcone under the above conditions gave only the corresponding flavylium salt and unconverted chalcone. The use of dilute base to effect isomerization gave only recovered chalcone. The flavylium chloride, after two precipitations from alcohol solution with absolute ether, was crystallized from dilute alcoholic hydrochloric acid, forming short, slender orange-red needles, m. p. 236–237° (dec.) after sintering and turning brown at 147–148°.

Anal. Calcd. for $C_{15}H_{11}O_3Cl$: C, 65.58; H, 4.04. Found: C, 65.39; H, 4.17.

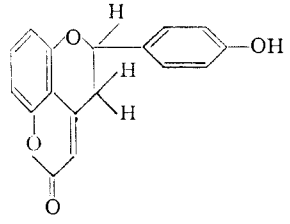
A dilute alcoholic solution of the flavylium chloride was colored deep carmine by sodium hydroxide solution. The dilute solution of the flavylium chloride in concentrated sulfuric acid exhibited a yellow-green fluorescence.

Eriodictyol by the Hydrogenation of Luteolin.—A solution of 0.80 g. of luteolin in 100 ml. of alcohol was reduced with the aid of 400 mg. of Adams platinum oxide. The mixture was shaken at 30–37 lb. sq. in. gage of hydrogen for five hours at room temperature. The filtered solution was evaporated to dryness and the orange oil, which could not be crystallized, acetylated with pyridine–acetic anhydride. The semi-crystalline acetylation product was fractionally crystallized several times from 90% alcohol and thus separated into two fractions. The least soluble fraction had m. p. 227–229° and proved to be luteolin tetraacetate. The second fraction, after repeated recrystallization from dilute alcohol, melted at 138–139° alone or mixed with an authentic sample of eriodictyol tetraacetate[7] and weighed 0.40 g.

Polyhydroxyflavanone Acetates.—The acetylation of a polyhydroxyflavanone by boiling with sodium acetate and acetic anhydride often leads to products other than the desired polyacetoxyflavanone.[8] A mild acetylation procedure is recommended; the most convenient is the use of pyridine and acetic anhydride at room temperature. Sodium acetate–acetic anhydride can be used if the mixture is heated just enough to bring about solution and then allowed to cool.

(7) Geissman, THIS JOURNAL, **62**, 3258 (1940).

(8) Upon heating a mixture of 50 mg. of 5,4′-dihydroxyflavanone, 1 ml. of acetic anhydride and 25 mg. of fused sodium acetate at 100° for one-half hour there was obtained a product crystallizing from dilute alcohol in long colorless needles, m. p. 144.5–145.0°. This compound did not respond to the usual color tests for flavanones. Analyses indicated mono-acetylation and dehydration; it was apparent that a Perkin-type reaction had ensued, with the formation of the bis-pyrone.



Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.87, 72.78; H, 4.95, 4.57. The monoacetate, prepared by treating the bis-pyrone with pyridine–acetic anhydride, crystallized from dilute alcohol in small colorless prisms, m. p. 133.5-4.0°.

Anal. Calcd. for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.72; H, 4.47.

Naringenin-4',7-dimethyl Ether.—To a suspension of 5.0 g. of naringenin in 25 ml. of methanol and 10 ml. of dimethyl sulfate was added, at room temperature and with stirring, a solution of 6.0 g. of potassium hydroxide in 20 ml. of 50% methanol. The addition was carried out over a one-hour period and stirring continued for an additional hour.

The colorless solid which was present was collected, washed, and recrystallized from methanol. The crude material weighed 3.8 g.; after purification it weighed 3.5 g. and melted at 118–119° (reported for naringenin-4',7-dimethyl ether,[9] m. p. 118°).

The filtrate and washings were acidified and extracted with ether, and the ether solution washed with 5% sodium carbonate solution. Acidification of the sodium carbonate extract yielded 1.0 g. of a compound which crystallized from methanol as buff leaflets, m. p. 187–188°. This was naringenin-4'-methyl ether.[10]

2',4',4-Trimethoxy-6'-hydroxychalcone.—A mixture of 19.7 g. of naringenin-4',7-dimethyl ether, 27 g. of methyl *p*-toluenesulfonate, 9.5 g. of anhydrous potassium carbonate and 50 ml. of dry xylene was heated under reflux for two hours. The pasty yellow reaction mixture was cooled, water was added and the xylene layer separated. The aqueous layer was acidified and extracted with ether, then discarded. The combined ether–xylene solution was washed thoroughly with 10% aqueous sodium hydroxide solution to remove 2',6'-dihydroxy-4,4'-dimethoxychalcone, and to it was added 75 ml. of 10% methanolic potassium hydroxide solution. To the resulting homogeneous solution was added 50 ml. of water and the alcoholic-aqueous layer separated. This procedure was repeated with 25 ml. of methanolic alkali.

The ether–xylene layer was washed with water, dried and evaporated to dryness. There was obtained 7.6 g. of 2',4',6',4-tetramethoxychalcone, m. p. 119–119.5° (reported,[11] m. p. 119–120°).

The alkaline extract was acidified and yielded 8.5 g. of 2',4',4-trimethoxy-6'-hydroxychalcone as long, bright yellow needles, m. p. 113.5–114° (reported[11,12], m. p. 113–114°). Comparable yields were obtained starting with naringenin instead of its dimethyl ether.

The methylation of 5 g. of hesperetin by the same procedure yielded 2.3 g. of 2',3,4,4',6'-pentamethoxychalcone and 3.1 g. of 2'-hydroxy-3,4,4',6'-tetramethoxychalcone.

Summary

Methods for the synthesis of polyhydroxychalcones and polyhydroxyflavanones are described. Eight new chalcones and ten new flavanones, and the acyl derivatives of each have been prepared.

(9) Shinoda and Sato, *J. Pharm. Soc. Japan*, **48**, 933 (1928); *Chem. Abs.*, **23**, 2956 (1929).

(10) Shinoda and Sato, *ibid.*, 791 (1928); *Chem. Abs.*, **23**, 836 (1929).

(11) Bargellini, *Gazz. chim. ital.*, **44**, II, 421 (1914); *Chem. Abs.*, **9**, 1042 (1915).

(12) Kauffmann and Kieser, *Ber.*, **46**, 3799 (1913).

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Flavanones and Related Compounds. II. The Colored Reduction Products of Polyhydroxyflavanones

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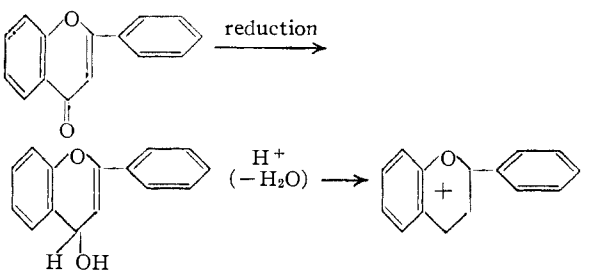
Among the methods used for the recognition and characterization of polyhydroxyflavanones and -flavones are certain reduction procedures which yield substances which are or can be converted into deeply colored compounds. The most noteworthy of these are the reduction with magnesium and hydrochloric acid,[1] and with sodium amalgam,[2] followed by acidification. The acidic reduction yields deeply colored products with flavanones and flavones while reduction with sodium amalgam gives deep colors with flavones and flavanones but not with flavonols (3-hydroxyflavones).[3] With a given substrate both procedures give colors which are visually very similar and often indistinguishable.

The belief has been expressed[1c,g,2d,e,g,i] or implied[2f] that the colored substances formed in both of these reduction procedures are flavylium salts. This view doubtless depends partly upon the superficial visual similarity of the colors produced to those of such typical flavylium salts as the anthocyanidins, but in some instances has foundation in the fact that anthocyanidins have actually been isolated as products of such reduction procedures.[2i,4,5]

The reduction of a flavone to a flavylium ion can be formulated plausibly as follows



(1) (a) Willstätter, *Ber.*, **47**, 2874 (1914); (b) Shibata, *Bot. Mag.*, **29**, 121 (1915); (c) Noack, *Z. Botan.*, **10**, 574 (1918); (d) Asahina Inubuse, *Ber.*, **61**, 1514 (1928); (e) Shinoda, Sato and Kawagoye, *J. Pharm. Soc. Japan*, **49**, 123 (1929); (f) Rangaswami and Seshadri, *Proc. Indian Acad. Sci.*, **16A**, 129 (1942); (g) Tasaki, *Acta Phytochim.*, **3**, 1 (1927); (h) Hattori, *ibid.*, **4**, 63 (1928).

(2) (a) Tiemann and Will, *Ber.*, **14**, 946 (1881); (b) Will, *ibid.*, **18**, 1311 (1885); (c) Jonesco, *Compt. rend.*, **180**, 1361, 1523 (1925); (d) Stein, *J. Biol. Chem.*, **88**, 351 (1862); *ibid.*, **89**, 280, 491 (1863); (e) Hlasiewetz and Pfaundler, *Sitzber. kgl. preuss. Akad. Wiss.*, **50**, 6 (1864); (f) Comb, *Compt. rend.*, **157**, 1002 (1913); (g) Asahina and Inubuse, *Ber.*, **61**, 1646 (1928); (h) Asahina, Nakagome and Inubuse, *ibid.*, **62**, 3016 (1929); (i) Asahina and Inubuse, *ibid.*, **64**, 1256 (1931).

(3) The colors are generally some hue of red, and depending upon the degree of hydroxylation may vary from orange-red to magenta, or, rarely, blue.

(4) Willstätter and Mallison, *Sitzber. kgl. preuss. Akad. Wiss.*, 769 (1914).

(5) Robertson and Robinson, *J. Chem. Soc.*, 2196 (1927).