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.

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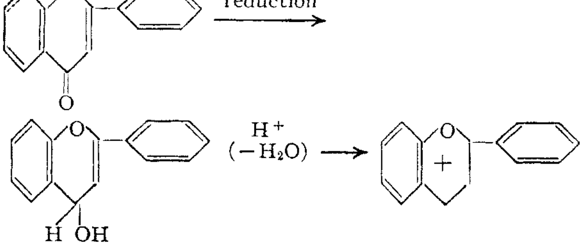
Flavanones and Related Compounds. II. The Colored Reduction Products of Polyhydroxyflavanones

By T. A. Geissman and R. O. Clinton

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



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[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).

The extent to which this reaction proceeds in the case of flavones has been a matter of controversy[6]; but it is clear that no such ready formulation is possible in the case of a flavanone, since a flavanone and its corresponding flavylium salt are at the same oxidation level. This was recognized by Asahina and Inubuse,[2g] who accounted for the production of flavylium salts in the sodium amalgam reduction of flavanones by postulating an oxidation (by air) following the reduction step. Such an oxidation in alkaline solution is not unreasonable in view of the observation of Kuhn and Winterstein[7] on the air oxidation of the leuco base of cyanidin; and that it might possibly occur in acid solution is indicated by the results of Baker[8] on the air oxidation of anhydrocatechol to the corresponding isoflavylium salt.

The use in this Laboratory of both the magnesium–hydrochloric acid and sodium amalgam reduction procedures as qualitative tests in studies on naturally-occurring substances has led in the course of time to the conviction that the colored substances produced are not typical flavylium salts. This was particularly true of the magnesium–hydrochloric acid reduction of flavanones and of the sodium amalgam reduction of both flavones and flavanones. The present study was undertaken for the purpose of examining these reduction procedures in detail, both by spectrophotometric means and by the isolation of identifiable reduction products. A secondary purpose of the work was to accumulate sufficient spectral data to serve as a basis for identifying known flavanones and for predicting the structures of new ones. The latter object was not achieved with complete success since it was found that the colors tended to be unstable and thus to make it difficult to reproduce extinction coefficients with satisfactory precision, and often showed too little variation with structural changes.

It was recognized at the start that the reduction of a flavanone could give rise to a number of possible reduction products, many of which would be expected to yield colored salts upon treatment with acids. This complexity in what might at first appear to be a rather simple reaction (*i. e.*, reduction of the carbonyl group) is due to the fact that flavanones in solution readily isomerize to chalcones and these may undergo 1,2-, 1,4- or several kinds of bimolecular reduction. It was for this reason that catalytic hydrogenation of the flavanones in an aprotic solvent was used as a reference method; it was assumed that by this method the predominant reaction would be straightforward reduction of the flavanones to 4-hydroxyflavones.

Data and Results

In Table I are given the maxima and minima in the absorption spectra of the colored reduction products of the flavanones examined.[9] These data were taken on the solutions obtained as described in the Experimental part, and do not necessarily represent pure substances. In fact, as will be shown below, a variety of compounds may be present, depending upon the method of reduction.

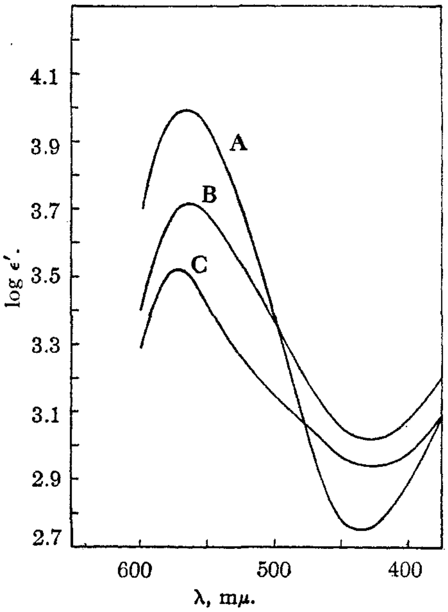

Fig. 1.—Reduction of 4',7,8-trihydroxyflavanone: A, cat. H_2; B, sodium amalgam; C, Mg–HCl.

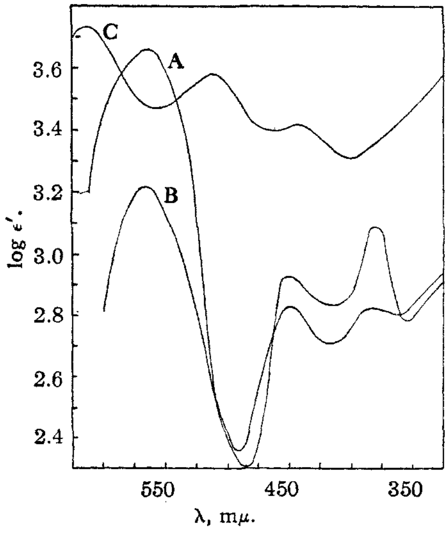

Fig. 2.—Reduction of 4'-hydroxyflavanone: A, cat. H_2; B, sodium amalgam; C, Mg–HCl.

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(6) Malkin and Nierenstein, THIS JOURNAL, **52**, 2864 (1930); *Ber.*, **64**, 1976 (1931); Robertson and Robinson, *J. Chem. Soc.*, 1530 (1928); Kuhn and Wagner-Jauregg, *Ber.*, **61**, 2506 (1928).

(7) Kuhn and Winterstein, *Ber.*, **65**, 1742 (1932).

(8) Baker, *J. Chem. Soc.*, 1593 (1929).

(9) 3',4'-Methylenedioxy-, 3',4'-dimethoxy-, 5,7-dimethoxy-, 2',6-dihydroxy- and 2'-hydroxyflavanone gave no reproducible colors by any of the reduction methods used.

TABLE I

SPECTRA OF THE MIXTURE OF COLORED PRODUCTS DERIVED FROM FLAVANONES BY VARIOUS REDUCTION METHODS[a]

Flavanone substituents						Catal. hydrog.[b]				Na–Hg[c]				Mg–HCl[c]			
						Max.		Min.		Max.		Min.		Max.		Min.	
5	7	8	2'	3'	4'	mμ	ε'	mμ	ε'	mμ	ε'	mμ	ε'	mμ	ε'	mμ	ε'
OH	OH				OH	539	11650	391	250	539[h]	4260	390	300	525[h]	4130	401	797
OH	OH			OH	OH	556	5930	384	396	555[h]	2120	381	300	550[h]	3470	420	839
OH	OH			OCH_3	OH	554	15320	414	936	554[h]	5500	420	1190	547[h]	4640	416	828
OH	OH			OH	OCH_3	549	7620	382	660	548[h]	2350	395	540	527	1850	422	620
OH	OH				OCH_3	531	15860	381	307	530	5130	390	159	512	2190	400	615
OH	OCH_3				OCH_3	542	31000	383	460	542	9020	380	560	519	5500	398	1000
OCH_3	OCH_3				OCH_3	556	39640	376	98	554[h]	12610	379	125	518[h]	1410	425	697
OCH_3	OCH_3			OCH_3	OCH_3	566	53000	377	1750	566	14810	380	1205	538[h]	6050	372	80
					OH	565[d]	1630	490	226	565[d, h]	4570	485	200	615[h,i]	5370	550	2930
	OH				OH	566	11400	385	640	568[h]	5670	395	2810	563[h]	4100	412	1190
	OH				OCH_3	562	36100	381	394	562	11050	391	200	562	7220	385	1400
	OH				OC_2H_5	565	28500	380	456	564	9010	380	311	557	4520	398	1560
	OH	OH				588	340	515	248	586	1580	514	681	566	1640	470	1420
	OH	OH	OH			...				...				617[o]	1400	607	1315
	OH	OH			OH	565	9810	435	560	562	5200	428	1040	569	3350	426	860
	OH	OH		OH	OH	591	5040	440	1210	589[h]	3460	440	982	592[h]	4000	437	1340
	OCH_3				OCH_3	570	12700	380	264	570[h]	1550	390	502	576[h, l]	3160	530	887
	OH			OH	OH	584[e]	22500	454	1900	584[e, h]	11010	462	980	589[h]	2140	446	641
				OH	OH	649[f]	160	509	59					...			
					OCH_3	572[g]	1280	504	179					...			
	OH													578[j]	3160	481	1225
	OCH_3				OH									548[h,k]	2340	512	1900
	OCH_3													590[m]	2040	500	1195
	OH			OH										510[n]	2190	493	2000
	OH			OCH_3	OH									582	6430	439	1820
	OH	OH		OCH_3	OCH_3									586	5480	369	740
OH					OH									565[h]	8160	404	1360

[a] See footnote 15 for the definition of ε'. [b] Solvent: dioxane–concentrated hydrochloric acid. [c] Solvent: amyl alcohol–concentrated hydrochloric acid. [d] Further maxima at 449, 383 mμ, minima at 415, 360 mμ. [e] Further maximum at 386 mμ, minimum at 363 mμ. [f] Further maximum at 403 mμ, minimum at 360 mμ. [g] Further maximum at 447 mμ. [h] Anaerobic reduction gave maxima and minima identical within experimental error. The greatest variance in anaerobic ε' values was 14% in the sodium amalgam reduction and 8% in the magnesium–hydrochloric acid reduction [i] Further maxima at 512, 445 mμ, further minima at 460, 402 mμ. [j-o] Further maxima at 443, 489, 478, 420, 447, 539 mμ, respectively, further minima at 432, 425, 405, 360, 373, 418 mμ, respectively.

The most striking result of these experiments is the discovery that the substances produced by catalytic hydrogenation and by sodium amalgam reduction give, upon treatment with acids, colors which are spectrally identical.[10] The colored substances formed by magnesium–hydrochloric acid reduction are, on the other hand, different from these in some cases and the same in others, although there is almost always a close visual resemblance. These observations are demonstrated more clearly by reference to Figs. 1 and 2 which show the complete absorption spectra for the solutions derived from two of the flavanones used.

The fact that identical spectra were obtained for the products derived from sodium amalgam reductions carried out both in air and in purified nitrogen proves that no oxidation step such as was suggested by Asahina[2g] is necessary to explain the appearance of colored substances. The same result was obtained in the case of magnesium–hydrochloric acid reduction.

Several properties of the colored substances which were present in the final acid solutions give clear indication that they are not flavylium salts, and make it doubtful that any flavylium salts are present even as minor components of the mixtures. For one thing, relatively high acid concentrations are necessary to develop the full colors, and when amyl alcohol solutions of the colored substances are washed with water until neutral the colors fade until they finally become orange to yellow.[11] This salt–base equilibrium is readily reversible. The colors are only moderately stable, whereas flavylium salts, such as anthocyanidins, can be preserved in solution for considerable periods of time without change. The most convincing evidence of this point, however, is found in the colors themselves, which are in every case deeper (*i. e.*, have absorption maxima at longer wave lengths) than the flavylium salts of corresponding structure. In Table II are given the absorption maxima of a number of flavylium salts and those of the reduction products of the flavanones of corresponding structure.

Large scale reductions were carried out on flavanone and on 4',5,7-trimethoxyflavanone. The reduction of flavanone has been described by Karrer, Yen and Reichstein[12] and by Mozingo and Adkins,[13] who prepared in this way α-[12] and β-4-hydroxyflavane.[12,13] In the present work,

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[10] Because of the fact that most of these absorption spectra possess broad, rather flat maxima and minima a difference of as much as 3 mμ cannot be considered significant, particularly since many of the colors are unstable enough so that it was not possible to prolong the measurements sufficiently to fix the maxima with high precision.

[11] The true pseudo-bases are probably colorless, the yellow colors being due probably to traces of chalcones which are generally present in the mixtures resulting from the reduction procedures.

[12] Karrer, Yen and Reichstein, *Helv. Chim. Acta*, **60**, 669 (1938).

[13] Mozingo and Adkins, THIS JOURNAL, **60**, 669 (1938).

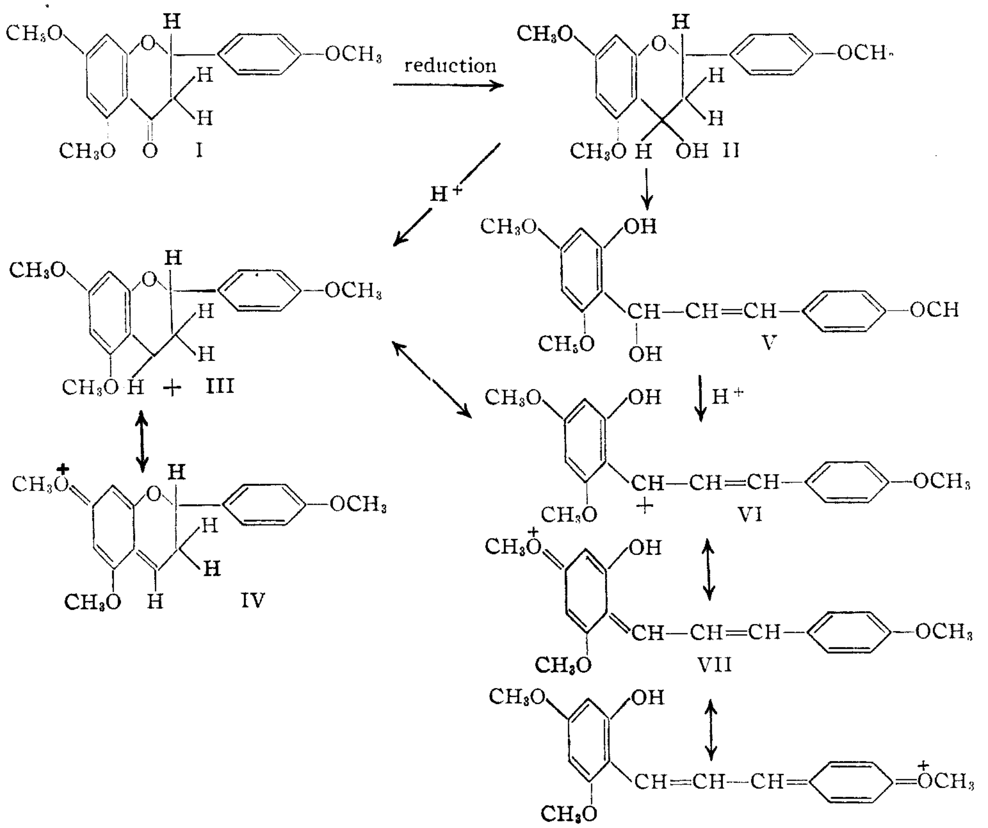
TABLE II

Flavanone	Flavanone reduct. prod.[a] λ max., mμ	Flavylium salt[b,c] μ max., mμ
4′-Hydroxy	565	468
4′,7-Dihydroxy	566	469
4′-Methoxy-7-hydroxy	562	469
4′,7,8-Trihydroxy	565	476.5
4′,5,7-Trihydroxy	539	476.5
4′,5,7-Trihydroxy-3′-methoxy	554	500

[a] Catalytic hydrogenation values. Solvent: dioxane–hydrochloric acid. [b] Hayashi, *Acta phytochim.*, **7**, 117, 143 (1933); **8**, 65, 179 (1935); **8**, 1 (1936); Schou, *Helv. Chim. Acta*, **10**, 907 (1927). [c] Solvent: alcohol–hydrochloric acid.

the catalytic hydrogenation of flavanone also yielded β-4-hydroxyflavane; sodium amalgam reduction yielded β-4-hydroxyflavane and the pinacol[14] formed by bimolecular reduction of flavanone, along with some 2′-hydroxychalcone formed by ring opening of flavanone; magnesium–hydrochloric acid reduction yielded the pinacol, α-4-hydroxyflavane and some of the chalcone. In the latter case the pinacol was the chief (isolated) product, while with sodium amalgam β-4-hydroxyflavane predominated.

The catalytic hydrogenation of 4′,5,7-trimethoxyflavanone formed β-4-hydroxy-4′,5,7-trimethoxyflavane. The pure flavane, when treated with hydrochloric acid, gave a deep carmine color which was spectrally identical with the color of the solution prepared by reducing the trimethoxyflavanone with sodium amalgam, anaerobically and in air (pure flavane: $\lambda_{max.}$ 556 mμ, ϵ'[15] 40900, $\lambda_{min.}$ 374 mμ, ϵ' 43; sodium amalgam reduced solution: $\lambda_{max.}$ 554 mμ, ϵ' 12600, $\lambda_{min.}$ 379 mμ, ϵ' 125, in air; $\lambda_{max.}$ 554 mμ, ϵ' 12000, $\lambda^{min.}$ 377 mμ, ϵ' 100, anaerobically). The reduction of 4′,5,7-trimethoxyflavanone with sodium amalgam led to the isolation of the same flavane derivative; present also in the solution after the reaction was interrupted was 2′-hydroxy-4′,6′,4-trimethoxychalcone. In each case oils, which also gave colors with acids, were also obtained.



That chalcones may also lead to reduction products which can give rise to colored salts was shown by the reduction with sodium amalgam of 2′,4′,6′,3,4-pentamethoxychalcone. This reaction yielded a colorless crystalline compound to which has been assigned the structure of the pinacol formed by bimolecular reduction of the chalcone. When this substance was treated in solution with concentrated hydrochloric acid it gave a deep

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[14] Freudenberg and Orthner, *Ber.*, **65B**, 1748 (1932).

[15] ϵ' values given are based on the usual type of equation $\epsilon' = (1/cd) \log_{10} (I_0/I)$. However, in the present case values of ϵ' are not true molar extinction coefficients, since the total concentration of the colored substances is unknown. The values given are based upon assumed complete reduction of an initial concentration c of flavanone and, therefore, tend to represent a minimum extinction coefficient for a given colored monomolecular species. The application of Beer's law was shown experimentally.

carmine coloration, deeper and more intense than the orange-red color given by the original chalcone under the same conditions. The color developed was too fleeting for spectral purposes.

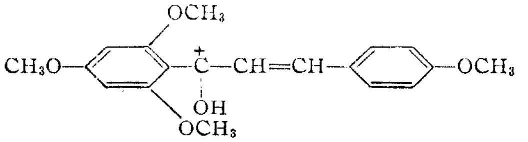
Discussion

The foregoing results indicate that the reduction of flavanones by sodium amalgam or by magnesium and hydrochloric acid does not lead to flavylium salts but to a complex mixture of products among which are flavanes and pinacols derived from simple and bimolecular reduction, and which may contain reduction products of the chalcones to which the flavanones are known to isomerize under the conditions of the reactions.

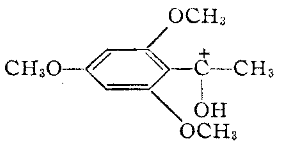
The formation with acidic reagents of colored compounds from the substituted 4-hydroxyflavanes and the pinacols, as well as from certain of the possible chalcone reduction products, can be readily explained. Taking as an illustrative example the products derived from 4′,5,7-trimethoxyflavanone (I), the 4-hydroxyflavane would have the structure II. Under the influence of a strong acid this could give rise to the carbonium ion III, which could be stabilized by resonance among forms such as IV, etc. Isomerization of II to V, which could also be derived from the chalcone isomeric with I by direct reduction, leads to cation VI, which bears a formal resemblance to such colored substances as dyes of the triphenylmethane series and to flavylium salts. Resonance of VI among such forms as VII, etc., or of III–IV, would obviously be strongly influenced by the nature, number and position of the substituents in both aromatic nuclei.

Similar resonating cations can be derived from bimolecular reduction products of both flavanones and chalcones, and probably contribute to the colors produced in the reduction procedures described.

It appears likely that such ions as VII contribute more to the color than such structures as IV because of the greater length of the conjugated system involved in the resonating system of VII. While it would be difficult to demonstrate this, since it would be expected that the interconversion of III and VI takes place readily in the presence of acids, indirect evidence that such is the case is found in the observation, made in the course of other studies in this Laboratory, that the ion VIII resulting from coördination of a proton with a chalcone has a deeper color than the ion IX derived in the same way from 2,4,6-trimethoxy-acetophenone.



VIII



IX

The correspondence between the colors produced from the products of catalytic hydrogenation and of sodium amalgam reduction, coupled with the fact that the conditions of the catalytic reduction were such as to minimize the formation of products derived from the chalcones, leads to the conclusion that in these methods the colored substances are indeed derived from the 4-hydroxyflavones such as II. Since reduction of flavanone itself by means of magnesium and hydrochloric acid leads to the pinacol as the predominant product, and since the colors produced by reduction in this way of polyhydroxyflavanones correspond in some cases only with those obtained by the other two methods, it may be assumed either that the magnesium–hydrochloric acid colors are due to products other than those corresponding to II, or that under the acid conditions prevailing products such as II, III, V, etc., are changed into other substances.

It is recognized that the scheme I–VII may be an over-simplification and that while products such as II may be the direct products of the reduction step, treatment with strong acid for the purpose of producing the colored salts may bring about changes which result in the formation of colored substances other than VI–VII. However, there is at present no evidence that the simpler explanation is not the correct one. The present results do show that the colors produced in the color tests under consideration are not due to the formation of anthocyanidins or flavylium salts, that an oxidation step is not necessary to explain the formation of these colored substances and that simple substances, such as properly substituted 4-hydroxyflavanes, can give rise to deeply colored substances by treatment with acids.

Experimental[16]

I. Reduction for Spectrophotometric Measurements

A. Catalytic Hydrogenation.—Twenty to 100 mg. of the dry, purified flavanone was weighed into a 50-ml. volumetric flask and 100 mg. of Adams platinum oxide was added. To this mixture was added 25 ml. of purified anhydrous dioxane[17] and the flask contents were hydrogenated at room temperature and a pressure of 1 atm. of hydrogen until 1 mole of hydrogen had been absorbed by the flavanone. The reduced solution was made up to volume with dioxane and filtered, and portions of the final solution treated with concentrated hydrochloric acid (5 ml. to 10 ml. of dioxane solution) to develop the color. The color was also developed by other strong acids such as concentrated sulfuric, *p*-toluenesulfonic, chloroacetic, etc., but hydrochloric acid was used in the routine procedure.

B. Sodium Amalgam Reduction. 1. In Air.—To 10 ml. of a 0.001 molal solution of the flavanone in 50%

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(16) All melting points are corrected. Spectra were determined by means of the Beckman Quartz Spectrophotometer.

(17) Hess and Frahm, *Ber.*, **71**, 2627 (1938); *cf*, Eigenberger, *J. prakt. Chem.*, **130**, 75 (1931).

alcohol was added 3 g. of 3% sodium amalgam, while maintaining the temperature at 45° and allowing a slow stream of air to pass through the solution. After twenty minutes a second 3-g. portion of sodium amalgam was added and the reaction allowed to continue fifteen minutes longer. The solution was decanted from the amalgam, which was thoroughly washed with dilute alcohol, and acidified with 5 ml. of concentrated hydrochloric acid. The deeply colored solution was diluted with about 60 ml. of water and shaken with 10 ml. of redistilled amyl alcohol. The amyl alcohol layer, now containing all of the color, was washed with two 60-ml. portions of cold water, dried superficially over anhydrous sodium sulfate, and transferred to a 50-ml. volumetric flask. The aqueous solutions were extracted with further small portions of amyl alcohol. The combined amyl alcohol extracts were made up to 50 ml. with amyl alcohol which had been used to wash the sodium sulfate with which the extracts had been treated. The final solution was usually a light yellow to orange in color. It was stored at 5–10° until absorption spectra were taken. For spectrophotometric purposes, 10 ml. of the amyl alcohol solution was treated with 5 ml. of concentrated hydrochloric acid to develop the color.

2. **In Nitrogen.**—Into a 200-ml., round-bottomed 3-necked flask, equipped with two 25-ml. dropping funnels, a gas inlet tube reaching to the bottom, and a gas outlet tube leading to a mercury-sealed outlet, was introduced 6 g. of powdered 3% sodium amalgam. Each of the separatory funnels was equipped with gas inlet and outlet tubes. All rubber stoppers were paraffined into place. Into one funnel was placed 10 ml. of a 0.001 molal solution of the flavanone in 50% alcohol and into the other 25 ml. of concentrated hydrochloric acid. Nitrogen, freed of the last traces of oxygen by passage through a tower containing the sodium ketyl of benzophenone[18] was led through all parts of the system for two hours, after which the exit gas no longer decolorized a dilute sodium ketyl solution, and then for an additional two hours. While maintaining a nitrogen flow of about one bubble per second, the flavanone solution was allowed to flow into the flask. After allowing the reaction to proceed for an hour at 40° the hydrochloric acid was run in; the deep color of the reduction product developed instantly. The solution was decanted into a separatory funnel and the color transferred quantitatively to amyl alcohol as described above.

C. **Magnesium–Hydrochloric Acid Reduction.**—To 5 ml. of a 0.001 molal solution of the flavanone in alcohol, contained in a 6″ test-tube, was added enough magnesium turnings to come to the liquid level, and to it was added 2 ml. of a solution of 60 g. of hydrogen chloride in 100 ml. of absolute alcohol. The mixture was stirred at intervals and kept at about 25° by occasional cooling in ice. After fifteen minutes an additional 2 ml. of the acid solution was added and the reduction allowed to proceed for ten minutes longer.

The solution was filtered through cotton and the cotton and excess magnesium washed thoroughly with dilute alcohol. The colored product was then transferred quantitatively to amyl alcohol as detailed for the sodium amalgam reduction procedure and absorption spectra measured in the same way.

Reduction with magnesium and hydrochloric acid was also carried out under strictly anaerobic conditions; color development was immediate and the colors were visually and spectrophotometrically identical with those developed in the presence of oxygen.

II. Isolation of the Products of Reduction

A. **The Reduction of Flavanone. 1. Catalytic Hydrogenation.**—A mixture of 464 mg. of flavanone, 166 mg. of Adams catalyst and 25 ml. of dioxane was hydrogenated as described above. One mole of hydrogen was taken up in twenty-six hours. The dioxane solution was filtered and evaporated to dryness in a current of air at room temperature. Recrystallization of the crystalline residue from benzene yielded β-4-hydroxyflavane, m. p. 148–149° (lit.,[12,13] m. p. 148°). The monoacetate melted at 97–98° (lit.,[12] 98°). The yield was substantially quantitative.

2. **Sodium Amalgam.**—To a solution of 1.0 g. of flavanone in 75 ml. of 70% alcohol was added 6.0 g. of 3% sodium amalgam in small portions over a period of two hours, at room temperature. The solution was filtered, acidified and diluted with water to 200 ml. The pale-yellow, semicrystalline precipitate was collected and washed with water. The air-dried material was triturated with benzene and the insoluble portion (10 mg.) recrystallized from glacial acetic acid. It formed small, colorless prisms, m. p. 255–256° (lit.,[14] bis-pinacol, m. p. 250°).

The benzene extracts were evaporated to dryness and the residue taken up in ether. Alkaline extraction of the ether solution yielded 320 mg. of 2′-hydroxychalcone, m. p. 87.5–88° (no depression when mixed with an authentic sample), and 128 mg. of an oil which could not be crystallized.

The alkali-washed ether solution was evaporated to dryness and from the residue was obtained 410 mg. of β-4-hydroxyflavane, m. p. and mixed m. p. with the product obtained by catalytic hydrogenation, 148–149°· acetate, m. p. 97–98°.

3. **Magnesium–Hydrochloric Acid.**—Into a 200-ml. 3-necked flask equipped with a stirrer and dropping funnel was introduced 4 g. of magnesium turnings and a solution of 500 mg. of flavanone in 50 ml. of alcohol. The flask was immersed in an ice-bath and 10 ml. of concentrated hydrochloric acid was added over a period of thirty minutes, with constant stirring. Two further 10-ml. portions of acid were added in the same way, followed by 10 ml. of water. The resulting solution was diluted to 300 ml. with water and filtered. The solid which was collected was triturated with warm 30% alcohol and recrystallized from glacial acetic acid. The compound (286 mg.) formed small white prisms, m. p. 255–256°. It did not depress the melting point of the bis-pinacol derived from the sodium amalgam reduction of flavanone.

The alcoholic triturate was diluted with water and yielded a semicrystalline material which was recrystallized from benzene. The product (37 mg.) was α-4-hydroxyflavane, m. p. 119.5–120° (lit. m. p. 119°,[14] 120–120.5°[12]). The monoacetate melted at 82.5–83° (lit. 85–86°,[14] 83–84°[12]).

From the benzene mother liquors was isolated 15 mg. of 2′-hydroxychalcone, m. p. 87–88°.

B. **The Reduction of 4′,5,7-Trimethoxyflavanone. 1. By Catalytic Hydrogenation.**—The hydrogenation of 1.00 g. of 4′,5,7-trimethoxyflavanone with 0.25 g. of Adams catalyst was carried out as described above. A total of 1.2 moles of hydrogen was absorbed in seven hours. The solution was filtered and evaporated to small volume, and the resulting precipitate crystallized from alcohol. β-4-Hydroxy-4′,5,7-trimethoxyflavane formed slender white needles, m. p. 159–159.5°. It gave a deep carmine color when treated with concentrated hydrochloric acid; this color was spectrally identical with that obtained when 4′,5,7-trimethoxyflavanone was reduced with sodium amalgam, and with that given by the 4-hydroxy-4′,5,7-trimethoxyflavane isolated from the reduction of 4′,5,7-trimethoxyflavanone or 4′,5,7-trimethoxyflavone[19] with sodium amalgam. It gave no color with alcoholic sodium hydroxide, even on heating.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; OCH_3, 29.43. Found: C, 68.27; H, 6.31; OCH_3, 29.23.

The monoacetate crystallized from benzene in short, slender white needles, m. p. 128–128.5°. It gave a deep red color with concentrated hydrochloric acid.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.89; H, 6.29.

2. **Sodium Amalgam.**—To a stirred solution of 2.0 g. of 4′,5,7-trimethoxyflavanone in 100 ml. of 50% alcohol was added 50 g. of 3% sodium amalgam. The mixture was

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[18] The nitrogen was pre-purified by passage through Fieser's solution. See Fieser, "Experiments in Organic Chemistry," D. C. Heath. N. Y., 1941, p. 395–396, for description of methods.

[19] Geissman and Clinton, This Journal, 68, 706 (1945).

stirred for one-half hour at 40–45°, an additional 50 g. of sodium amalgam was added and the mixture allowed to stand for six hours at room temperature (without stirring). The yellow solution was filtered, heated to boiling and diluted with water until a permanent turbidity appeared. Upon cooling an amorphous, light yellow precipitate formed. This was crystallized from dilute alcohol, and formed colorless crystals (612 mg.), m. p. 158–159°. It did not depress the m. p. of β-4-hydroxy-4′,5,7-trimethoxyflavane obtained by catalytic hydrogenation. The monoacetate melted at 127–128°; mixed m. p. 127–128°.

The alkaline mother liquor from which the flavane separated was acidified, and yielded, after purification, 204 mg. of 2′-hydroxy-4′,6′,4-trimethoxychalcone, m. p. and mixed m. p. with an authentic specimen, 114–115° (lit.,[20,21] 113–114°). The carbon bisulfide mother liquor from which the chalcone was crystallized yielded upon evaporation 1.04 g. of a yellow oil which afforded no crystalline material but which gave a deep carmine color with concentrated hydrochloric acid.

A repetition of the above procedure, except that the reduction was carried out under purified nitrogen, yielded 494 mg. of the β-4-hydroxyflavane and 115 mg. of the chalcone from 1.0 g. of the flavanone.

C. The Reduction of 2′-Hydroxy-4′,6′-trimethoxychalcone.—The reduction of 2.00 g. of 2′-hydroxy-4′,6′,4-trimethoxychalcone with sodium amalgam was carried out substantially as in the preceding example. There was isolated 473 mg. of β-4-hydroxy-4′,5,7-trimethoxyflavane, 650 mg. of unchanged chalcone and 600 mg. of a light yellow oil which gave a deep carmine color with concentrated hydrochloric acid.

D. The Reduction of 2′,4′,6′,3,4-Pentamethoxychalcone with Sodium Amalgam.—To a solution of 0.50 g. of 2′,4′,6′,3,4-pentamethoxychalcone in 80 ml. of 70% alcohol was added 10 g. of 3% sodium amalgam and the mixture allowed to stand at 50° for four hours. After the addition of a further 10 g. of sodium amalgam the reduction was allowed to proceed for another four hours at room temperature. The yellow solution was filtered and diluted with water. The oil which separated was rubbed with ether, with the formation of a colorless solid (37 mg.). This was crystallized from benzene, forming tiny, pale yellow needles, m. p. 234–236° dec. The compound gave an intense carmine color when treated with concentrated hydrochloric acid and instantly decolorized bromine in carbon tetrachloride solution. For these reasons the compound is formulated as the bis-pinacol of the chalcone rather than of the dihydrochalcone.

Anal. Calcd. for $C_{40}H_{46}O_{12}$: C, 66.84; H, 6.45; OCH_3, 43.17. Found: C, 66.59; H, 6.66; OCH_3, 42.95.

III. Attempted Isolation of Reduction Products from Polyhydroxyflavanones.—The reduction of hesperetin, naringenin, homoeriodictyol, liquiritigenin or 7-hydroxy-4′-ethoxyflavanone by any of the above methods did not lead to isolable products which could be identified.

Summary

The colored sodium amalgam reduction products of polyhydroxy- and polymethoxyflavanones are not flavylium salts, but are derived from a mixture of reduction products. Predominant among these are the 4-hydroxyflavanes resulting from reduction of the flavanone carbonyl group, and which it has been shown are converted into deeply colored substances upon treatment with strong acids.

LOS ANGELES, CALIFORNIA
RECEIVED SEPTEMBER 12, 1945

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

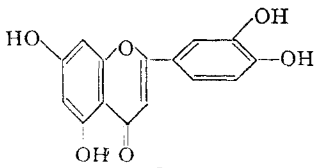
(21) Shinoda and Sato, *J. Pharm. Soc. Japan*, **50**, 265 (1930); *Chem. Abstr.*, **24**, 4046 (1930).

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

Flavanones and Related Compounds. III. The Reduction of Luteolin and Apigenin Trimethyl Ether with Sodium Amalgam

BY T. A. GEISSMAN AND R. O. CLINTON

When flavones such as luteolin (I) and apigenin trimethyl ether (II) are reduced with sodium amalgam and the reaction mixture acidified, deeply colored substances are formed



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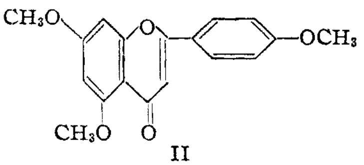
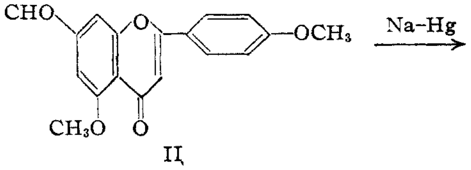


II

An analogous result is obtained when a flavonol such as rutin (quercetin-3-rutinoside) or quercetin pentamethyl ether (but not quercetin itself) is reduced[1] in the same way.

The simplest explanation of this reaction, and one that has been offered by Asahina,[1] is that the colored substances are flavylium salts, and that they arise by the reduction of the flavone carbonyl group to yield the pseudo-base III, which upon treatment with acid forms the flavylium ion IV. Taking the reduction of II as an example



II

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(1) Asahina and Inubuse, *Ber.*, **61**, 1646 (1928); **64**, 1256 (1931); Asahina, Nakagome and Inubuse, *ibid.*, **62**, 3016 (1929).