gave dark red needles (0.55 g.) of the ester, which did not melt below 360°.

Anal. Calcd. for $C_{26}H_{14}O_6$: C, 73.93; H, 3.34. Found: C, 73.82; H, 3.47.

Triangulene-4,8-quinone (VIII, R = R′ = H).—The dicarboxylic acids (VIII) (1 g.) were ground separately with copper powder (3 g.), and the mixtures heated under reduced pressure (10^{-4} mm.) at 260–270° for 10 hours. In both cases, a sublimate of dark red needles was obtained, which on crystallization from nitrobenzene yielded needles (0.3 and 0.25 g., respectively), whose properties were identical with those of a sample of triangulene-4,8-quinone prepared as described by Clar and Stewart.[1]

Dodecahydrotriangulene (IX).—Each of the dicarboxylic acids (VIII) (2 g.) mixed with red phosphorus (2 g.), potassium iodide (1 g.) and 55% hydriodic acid (20 ml.) was heated under pressure at 210° for 10 hours. When cold, the reaction mixtures were diluted with water and the precipitates filtered off, dried and ground with soda lime (4 g.). On heating under reduced pressure a clear, greenish fluorescent oil distilled which gave a white solid on cooling. Chromatographic purification (alumina) with petroleum ether (b.p. 40–60°) as eluant gave a colorless, non-fluorescent solution, which on concentration and recrystallization from methyl alcohol yielded clusters of colorless silky needles, (0.6 and 0.5 g., respectively), m.p. 162–163°. When this compound was admixed with an authentic sample of dodecahydrotriangulene, no depression in melting point was obtained.

GLASGOW, SCOTLAND

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

Basic Dissociation Constants of Some Substituted Flavones[1]

BY CHARLOTTE T. DAVIS AND T. A. GEISSMAN

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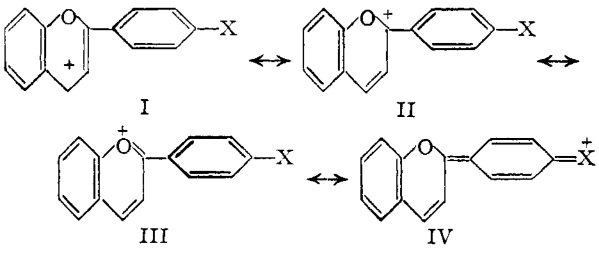
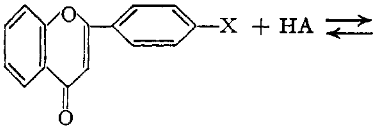
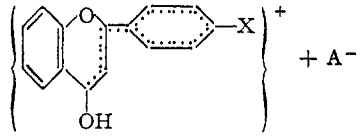
The pK_a values for five selected flavones have been determined by analyzing their absorption spectra in sulfuric acid solutions. Flavones are moderately strong oxygen bases, having pK_a values ranging from −0.8 for 4′-methoxyflavone to −2.45 for 2′,3,4′,6′-tetramethylflavone; these can be compared with the pK_a −6.0 for acetophenone. The importance of the chromone ring and the contribution of the 2-aryl group in stabilizing the protonated forms of these bases are shown by these data.

Early discussions of the structure of pyrilium and flavylium salts, centering about the question of the location of the positive charge,[2] can be resolved today into questions of the relative contribution to a resonance hybrid of such forms as the following (I–IV),[3] and the effects of substituents upon such a system. The importance of contributions corresponding to IV when the substituent X is methoxyl or hydroxyl is qualitatively evident from the pronounced bathochromic effects of such substituents upon the absorption maxima of flavones.[4] It is, however, difficult to interpret absorption spectra quantitatively in terms of the role of substituents in increasing the relative importance of quinonoid contributions in the 2-aryl group. A measure of the stabilizing effect of substituents (such as X in IV) upon forms such as IV is to be found in the equilibrium constant of the reaction







Effective participation of the 4′-substituent in distribution of the positive charge should affect the equilibrium constant measurably. Since such participation of a 4′-substituent requires a degree of coplanarity of the 2-aryl group with the benzopyrilium ring system, the introduction of 2′- and 6′-substituents represents another means of altering this equilibrium constant. In the present study five flavones have been examined with respect to the dependence of their basic strength upon their structures.

It has long been known that many pyrones, chromones and flavones form isolable salts with mineral acids,[5-7] but only in the cases of a limited number of substituted γ-pyrones[8,9] have the dissociation constants of bases of these classes been measured. Weak bases of other kinds have been extensively studied, chiefly by Hammett and his collaborators,[10] and their data on the acidity, expressed as the acidity function H_0, of sulfuric acid solutions have been used in the present work.

The use of absorption spectra in sulfuric and other strong acids in the determination of the basic dissociation constants of very weak bases has been

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(1) Flavanones and Related Compounds: Paper IX.

(2) For pertinent references, see R. L. Shriner and R. B. Moffett, THIS JOURNAL, **61**, 1474 (1939).

(3) These structures are selected as illustrative; when other substituents are present (*e.g.*, a carbonyl group at position 4), other structures may be equally important.

(4) B. Skarzynski, *Biochem. Z.*, **301**, 150 (1939).

(5) J. N. Collie and T. Tickle, *J. Chem. Soc.*, **75**, 710 (1899).

(6) H. Simonis, *Ber.*, **50**, 790 (1917).

(7) A. Schönberg and A. Sina, THIS JOURNAL, **72**, 1611 (1950).

(8) H. N. K. Rordam, *ibid.*, **37**, 577 (1915).

(9) E. I. Johnson and J. R. Partington, *J. Chem. Soc.*, 86 (1931).

(10) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932); L. P. Hammett and M. A. Paul, *ibid.*, **56**, 827 (1934); L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

widely applied[10,11-15] and the procedure adopted in this work does not differ in principle from the classical method. It consists essentially in interpreting the absorption spectra of the un-ionized and successively more ionized (in increasingly strong sulfuric acid solutions) forms of the base (B) under scrutiny, in such a manner as to permit the selection of that acid strength at which the compound is 50% ionized. From the expression[10] $H_0 = \log (B/BH^+) + pK_a$, $pK_a = H_0$ at 50% ionization. The acidity functions (H_0) have been determined for sulfuric acid solutions by Hammett, *et al.*,[10] and by Brand.[12]

Because of the many factors that affect the spectra, other than the ionization of the base alone, it was not found to be practicable to select by inspection either the spectrum of the pure species BH^+ or a wave length at which there existed a clearly discernable regular relationship between the degree of protonation and the extinction coefficient. The complexity of the spectra, particularly in their possession of two or more maxima or inflection points, and the absence of isosbestic points, is probably due in part to changes in the medium over the range of sulfuric acid concentrations used, and in some cases to the formation of diprotonated species at high acid strengths.

Typical spectra for the five flavones studied are shown in Figs. 1–5: Fig. 1, flavone; Fig. 2, 4′-methoxyflavone; Fig. 3, 2′,6′-dimethyl-4′-methoxyflavone; Fig. 4, 2′,4′,6′-trimethylflavone; and Fig. 5, 2′,3,4′,6′-tetramethylflavone.

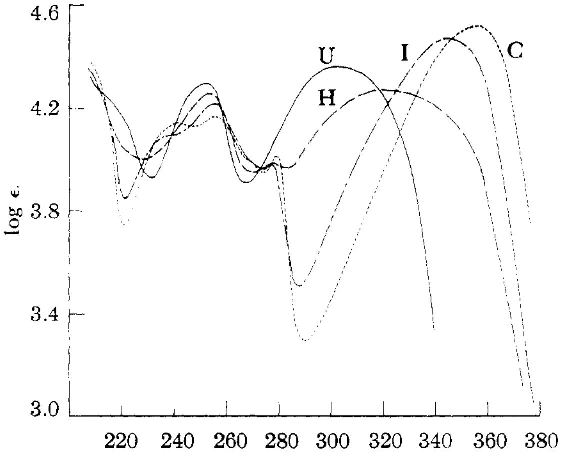

Fig. 1.—Absorption spectra of flavone: U, —, in water; H, — — — — — —, in 25.1% H_2SO_4; I, —.—.—.—, in 63.0% H_2SO_4; C, - - - - - -, in 91.5% H_2SO_4.

It should be noted that the possibility that sulfonation was occurring in strongly acid solutions of the two methoxylated flavones (the most susceptible) was examined with care. Although sulfonation was regarded to be unlikely, in view of the observations that 2,3-dimethylchromone was not sulfonated in 20% fuming sulfuric acid[16] and quercetin is sulfonated only upon heating with concentrated sulfuric acid,[17] it could not be assumed that 2′,6′-dimethyl-4′-methoxyflavone and 4′-methoxyflavone would be inert under all of the conditions used. However, experiment showed that a solution of the former in 93.8% sulfuric acid showed no appreciable alteration in its absorption spectrum during nine days at room temperature, and little change in over five months. Both of the flavones were recovered unchanged from 50% sulfuric acid solutions. Treatment of 2′,6′-dimethyl-4′-methoxyflavone with concentrated sulfuric acid in ether solution resulted in the formation of the crystalline flavylium hydrogen sulfate, from which the flavone could be recovered after treatment with cold water.

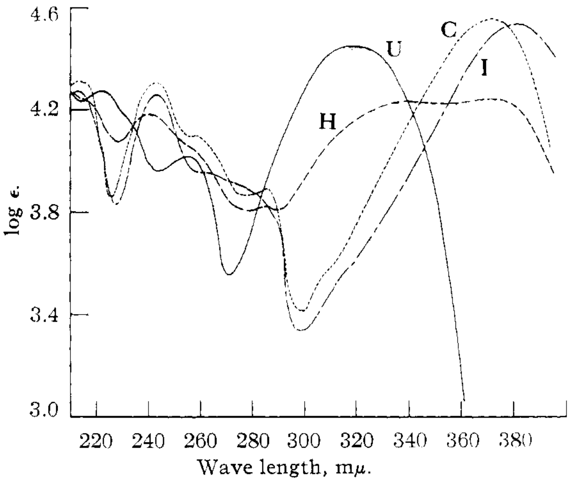

Fig. 2.—Absorption spectra of 4′-methoxyflavone: U, —, in 95% ethanol; H, — — — —, in 19.9% H_2SO_4; I, —.—.—.—., in 59.1% H_2SO_4; C, - - - - - -, in 93.3% H_2SO_4.

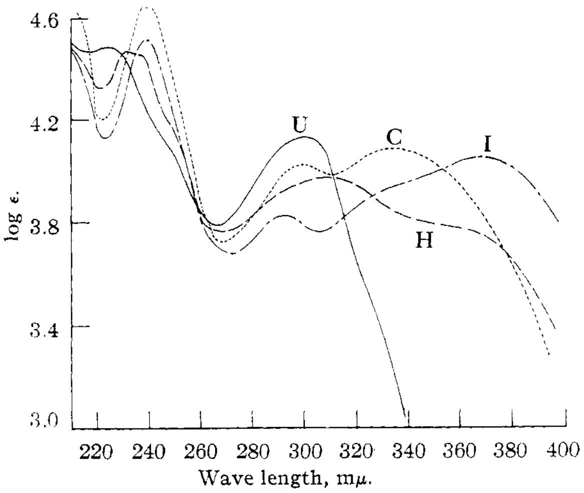

Fig. 3.—Absorption spectra of 2′,6′-dimethyl-4′-methoxyflavone: U, —, in 95% ethanol; H, — — — — — —, in 33% H_2SO_4; I, —.—.—.—, in 58.6% H_2SO_4; C, - - - - - -, in 93.8% H_2SO_4.

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(11) L. A. Flexser, L. P. Hammett and A. Dingwall, THIS JOURNAL, **57**, 2103 (1935).

(12) J. C. D. Brand, *J. Chem. Soc.*, 997 (1950).

(13) J. C. D. Brand, W. C. Horning and M. B. Thornley, *ibid.*, 1374 (1952).

(14) J. M. Hearn, R. A. Morton and J. C. E. Simpson, *ibid.*, 3329 (1951).

(15) J. L. Irvin and E. M. Irvin, THIS JOURNAL, **69**, 1091 (1947).

(16) H. Simonis, *Samml. Chem. Chemischtech. Vortrage*, **24**, 398 (1917).

(17) E. R. Watson and K. B. Sen, *J. Chem. Soc.*, **105**, 393 (1914).

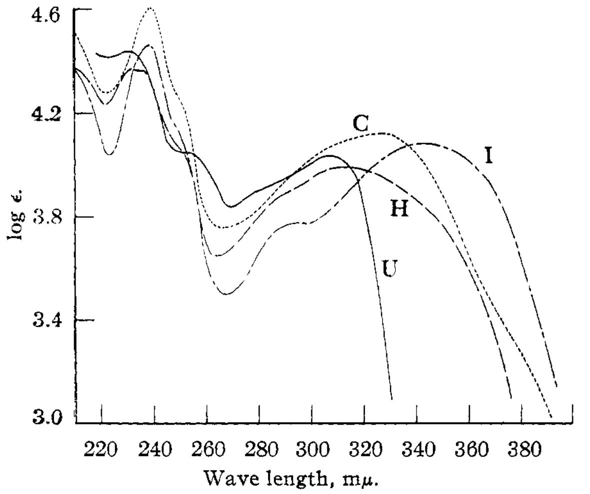


Fig. 4.—Absorption spectra of 2′,4′,6′-trimethylflavone: U, —, in 95% ethanol; H, — — — — —, in 36.2% H_2SO_4; I, —.—.—.—, in 66.5% H_2SO_4; C, - - - - -, in 93.1% H_2SO_4.

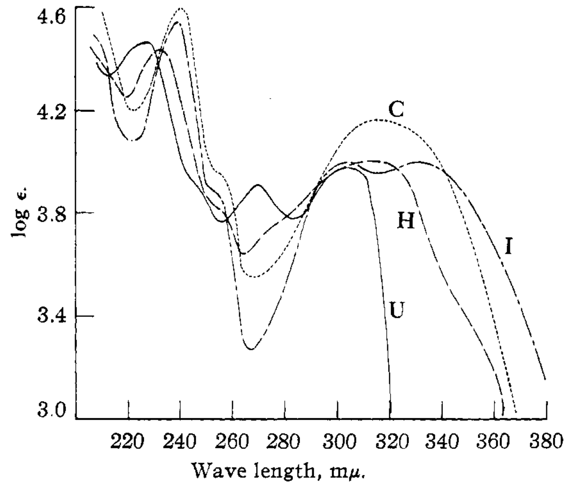


Fig. 5.—Absorption spectra of 2′,3,4′,6′-tetramethylflavone: U, —, in 95% ethanol; H, — — — —, in 42% H_2SO_4; I, —.—.—.—, in 68.6% H_2SO_4; C, - - - - - -, in 95.5% H_2SO_4.

The calculation of pK_a values from the spectral data was carried out as follows

I = fraction of the cpd. in the ionized form
λ_u = a selected wave length where $\epsilon_u \gg \epsilon_i$
λ_i = a selected wave length where $\epsilon_i \gg \epsilon_u$
ϵ = obsd. mol. extinction coefficient of a mixture of the ionized and un-ionized forms
ϵ_i = mol. extinction coefficient of the ionized form
ϵ_u = mol. extinction coefficient of the un-ionized form

If Beer's law holds under the experimental conditions used

$$(\epsilon)\lambda_i = (\epsilon_u)\lambda_i + [(\epsilon_i)\lambda_i - (\epsilon_u)\lambda_i]I \qquad (1)$$

$$(\epsilon)\lambda_u = (\epsilon_i)\lambda_u + [(\epsilon)\lambda_u - (\epsilon_i)\lambda_u][1 - I] \qquad (2)$$

Subtracting (2) from (1) and letting $(\epsilon)_{\lambda i} - (\epsilon)_{\lambda u} = D$

$$D = [(\epsilon_u)\lambda_i - (\epsilon_u)\lambda_u] + [(\epsilon_i)\lambda_i - (\epsilon_u)\lambda_i + (\epsilon_u)\lambda_u - (\epsilon_i)\lambda_u]I \qquad (3)$$

Since values such as $(\epsilon_u)_{\lambda i}$, etc., may be assumed to be nearly constant over a small range of acid concentration in the neighborhood of 50% ionization, the fraction ionized is linearly related to *D;* thus, $I = K + cD$, where

$$c = 1/[(\epsilon_i\lambda_i) - (\epsilon_u)\lambda_i + (\epsilon_u)\lambda_u - (\epsilon_i)\lambda_u]$$

and

$$K = [(\epsilon_u)\lambda_u - (\epsilon_u)\lambda_i]/[(\epsilon_i)\lambda_i - (\epsilon_u)\lambda_i + (\epsilon_u)\lambda_u - (\epsilon_i)\lambda_u]$$

Now, since H_1 = log [un-ionized/ionized] + pK_a

$$H_0 = 0.434 \ln \left[\frac{1 - cD - K}{K + cD}\right] + pK_a$$

The slope of the curve obtained by plotting D *vs.* H_0 is dH_0/dD, and at the inflection point

$$\frac{d^2H_0}{dD^2} = 0 = 0.434c^2\left[\frac{1}{(1 - cD - K)^2} - \frac{1}{(cD + K)^2}\right]$$

At the inflection point in this curve

$$1 - [cD + K] = cD + K$$

or fraction un-ionized = fraction ionized, and therefore $H_0 = pK_a$.

The wave lengths ϵ_i and ϵ_u were chosen close to the points of maximal difference between the extinction coefficients of the essentially un-ionized and practically completely ionized compounds. The inflection point of the H_0 *vs.* D curve was taken as the midpoint of the "straight" portion of the sigmoid curve. A curve showing a typical plot of H_0 *vs.* D for one of the five flavones studied is given in Fig. 6. In Fig. 7 is shown the curve, corresponding to Fig. 6, drawn from the reported spectral data[11] for acetophenone. The points secured from the spectral data fit best the curve calculated from the value of $pK_a = -6.05$ for this compound (*i.e.*, from: $H_0 = \log(B/BH^+) - 6.05$).

Although the method described appears to be the least subject to errors due to (1) the effects of medium changes upon absorption and (2) weighing of samples and measurement of solution volumes (since a difference in two extinction coefficients is used), there are a number of other ways in which spectral data may be related to acidity function to give a sigmoid, titration-like curve. We have observed that the use of extinction coefficients at a single wave length, and the areas (obtained by means of a planimeter) under the absorption spectrum plots between two arbitrarily selected wave lengths, when plotted against H_0, give curves from which pK_a may be estimated. In many cases the pK_a values obtained by these alternative methods agreed quite well with those derived from the more precise treatment, and gave *relative* values within the series of compounds that are in the same order.

The present method for evaluating basicity constants is simpler and probably more accurate than previously described procedures, and it is felt that the values for pK_a derived by its application to the five flavones are reliable to within less than 0.1 unit. It is difficult to attempt an estimate of a precise limit of error; but it is felt that in cases in which complex absorption spectra are found the second decimal in the pK_a values is of doubtful significance.

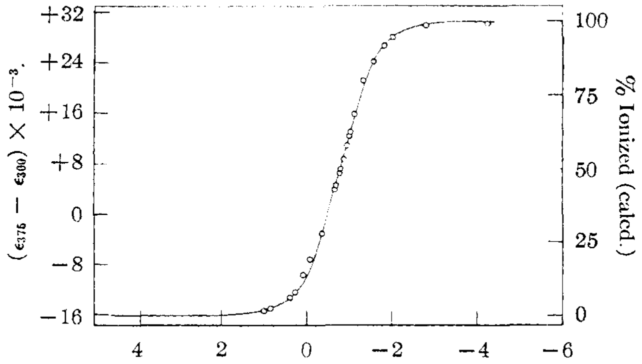


Fig. 6.—4′-Methoxyflavone: acidity function *vs.* ($\epsilon_{375} - \epsilon_{300}$); points from spectral data, curve calculated for pK_a − 0.8.

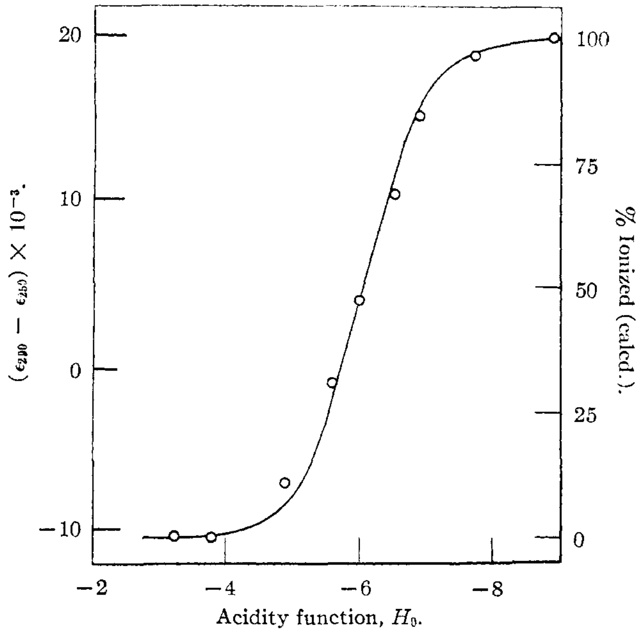


Fig. 7.—Acetophenone: acidity function *vs.* ($\epsilon_{290} - \epsilon_{250}$); points from spectral data (ref. 11); curve calculated for pK_a − 6.05.

Results.—The pK_a values for the five flavones are given in Table I.

TABLE I

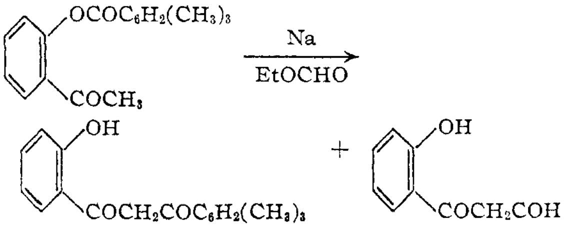
	Flavone	pK_a	λ_{max} (EtOH), mμ
A	4′-Methoxy	−0.8	325
B	Unsubstituted	−1.2	304
C	2′,6′-Dimethyl-4′-methoxy	−1.7	302
D	2′,4′,6′-Trimethyl	−2.05	296
E	3,2′,4′,6′-Tetramethyl	−2.45	304
	Acetophenone	−6.05[a]	..

[a] By recalculation of the data of Flexser, Hammett and Dingwall (ref. 11).

These results show clearly the importance of the 4′-methoxy group in affecting the basicity of the flavone system. When its ability to participate in forms such as IV is inhibited by the presence of 2′,6′-methyl groups the resulting flavone (C) is even more weakly basic than flavone itself (B), in which IV is possible but is not an important contribution to the hybrid. That the 4′-methoxyl group is exerting some effect even in (C) is shown by the diminution in base strength that occurs when the 2′,6′-methyl groups are present and the 4′-substituent is methyl (D); this compound (D) is a weaker base than (C). And when the resonance is even more inhibited by the presence of the 3-methyl group in addition to the three at the 2′,4′,6′-positions, the resulting flavone (E) is the weakest base of the series.

The considerably greater base strength of even the weakest of the five (E) than acetophenone shows the importance of the chromone ring to the basicity of flavones, and indicates that resonance of the kind shown in I–III contributes to the greatest degree to the stabilization of the cation. The superimposed effects of the 2-aryl group and the 4′-methoxyl group add relatively smaller increments of stability to the system, but nevertheless are important factors.

The preparation of the three new flavones (C, D, E) was accomplished by the use of methods that have found general application in flavone syntheses. The preparation of the diketone from which 2′,4′,6′-trimethylflavone was prepared presents a point of interest. The intramolecular acylation of *o*-(2,4,6-trimethylbenzoyloxy)-acetophenone in the solvent ethyl formate proceeded nearly completely in the direction of the intramolecular reaction; the amount of formylation of the acetyl group was very small as shown by the isolation, after ring closure, of only a few per cent. of chromone.[22]



Experimental

Spectrophotometry.—A sample of each flavone, weighed on a microbalance, was dissolved in about 50% sulfuric acid to make a 5 × 10^{-4} *M* stock solution from which 2 × 10^{-5} *M* solutions in various concentrations of sulfuric acid were prepared. Dilutions were made with conductivity water. The sulfuric acid was tested for optical clarity over the wave length range used, and the solvent blank was a sulfuric acid solution of the same concentration as that containing the compound. Measurements were made on a Cary Recording Spectrophotometer, Model 11 PMS. The concentration of sulfuric acid used in each measurement was determined by titration of a diluted aliquot with standard alkali. For spectra in "neutral" solution, samples of the flavones were dissolved in a small amount of alcohol and then diluted to volume with water. An aqueous solution of flavone sufficiently concentrated for measurement was obtained by dissolving it in water with warming for several hours. Aqueous and 95% ethanolic spectra were nearly identical, the former being shifted very slightly, with respect to the latter, toward the "ionized" spectra.

Recovery of Flavones from 50% Sulfuric Acid.—The stock solutions (5 × 10^{-4} *M*) of 4′-methoxy- and 2′,6′-dimethyl-4′-methoxyflavone were neutralized with potassium hydroxide. The flavones were collected by filtration and ether extraction (respectively), and found to be unchanged.

4′-Methoxyflavone[18] was prepared by selenium oxide oxidation of 2′-hydroxy-4-methoxychalcone. The flavone

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(18) F. Herstein and S. V. Kostanecki, *Ber.*, **32**, 318 (1899).

formed nearly white crystals, m.p. 158.5–159° (reported[19] 156°).

2,6-Dimethyl-4-hydroxybenzaldehyde.—A solution of 105 g. of hydrogen cyanide and 100 g. of 3,5-dimethylphenol in 300 ml. of dry benzene was cooled during the gradual addition of 100 g. of anhydrous aluminum chloride. Dry hydrogen chloride was passed into the stirred solution for 5 hours while temperature was maintained at 35–38°. The reaction mixture was poured into a large volume of ice and water, the aqueous mixture heated to boiling and cooled. The crystalline solid was collected and the filtrate extracted with ether. The ether was removed, the residual material combined with the solid fraction, and the whole steam distilled to remove the unreacted dimethylphenol (8 g.). The crude aldehyde was recrystallized from alcohol to yield 50 g. (45%) of product, m.p. 190–191° (reported[20] 189–190°).

2,6-Dimethyl-4-methoxybenzaldehyde was prepared by refluxing for 5 hours a mixture of 33 g. of 2,6-dimethyl-4-hydroxybenzaldehyde, 27 ml. of methyl iodide, 5.56 g. of sodium and 200 ml. of methanol. The reaction mixture was acidified and evaporated to dryness and the residue extracted with ether. The product (21 g.) melted at 47–48° (from ether); reported[21] 45–47°.

2,6-Dimethyl-2′-hydroxy-4-methoxychalcone.—To a solution of 17.2 g. of *o*-hydroxyacetophenone and 20.7 g. of 2,6-dimethyl-4-methoxybenzaldehyde in 200 ml. of ethanol was added 35 g. of 50% aqueous sodium hydroxide. After two days at room temperature the mixture was added to a mixture of 40 ml. of concentrated hydrochloric acid and 200 g. of ice. The solid (16.6 g.) was collected and recrystallized from alcohol. The compound (12 g.) formed shining yellow prisms, m.p. 125–125.5°; absorption in ethanol: maxima 370 (log ϵ 4.42), 250 (4.20); minima 296 (3.65), 230 (4.06).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.38; H, 6.64.

2′,6′-Dimethyl-4′-methoxyflavone.—A solution of 7.0 g. of 2,6-dimethyl-2′-hydroxy-4-methoxychalcone and 7.0 g. of selenium dioxide in 70 ml. of ethanol was refluxed for 13 hours. The filtered solution was evaporated under reduced pressure and the residual flavone crystallized from ethanol. It (5.0 g.) formed white leaflets, m.p. 122.5–123°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.86; H, 5.94.

***o*-Acetylphenyl 2,4,6-Trimethylbenzoate.**—A solution of 14.1 g. of 2,4,6-trimethylbenzoyl chloride and 6.8 g. of *o*-hydroxyacetophenone in 15 ml. of dry pyridine was allowed to stand at room temperature for 12 hours. The pyridine was removed under reduced pressure and the residue stirred with 50 ml. of 5% hydrochloric acid. The product was collected, washed with dilute alkali and water and recrystallized from methanol–petroleum ether. There was obtained 9 g. of the ester, m.p. 68.5–69.5°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.59; H, 6.37.

***o*-Hydroxy-ω-2,4,6-trimethylbenzoylacetophenone.**[22]—A solution of 5.64 g. of *o*-acetylphenyl mesitoate in 40 ml. of dry ethyl formate was treated with 0.9 g. of powdered sodium. After 12 hours the mixture was treated with ice and hydrochloric acid, and extracted with ether. Removal of the ether and recrystallization of the product from alcohol afforded 5.23 g. of the diketone, m.p. 73.5–74°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.48.

2′,4′,6′-Trimethylflavone.—A solution of 23.4 mg. of *o*-hydroxy-ω-2,4,6-trimethylbenzoylacetophenone in a mixture of 0.5 ml. of ethanol and 0.1 ml. of concentrated sulfuric acid was warmed on the steam-bath for three hours. The cooled solution was diluted with water and the precipitated flavone collected and recrystallized from ethanol. The compound formed colorless needles, m.p. 116–117°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.80; H, 6.10. Found: C, 81.48; H, 6.10.

2′,3,4′,6′-Tetramethylflavone was prepared by a method analogous to those employed in related syntheses by Nagai[23] and Zaki and Azzam.[24] To a mixture of 2.4 g. of *o*-hydroxy-ω-mesitoylacetophenone and 2.1 ml. of methyl iodide was added a solution of 0.39 g. of sodium in 15 ml. of dry methanol. The mixture was heated under reflux for 4 hours, acidified and evaporated under reduced pressure. The oily residue was not purified, but was warmed under nitrogen with 8 ml. of 48% hydriodic acid. The cooled solution was diluted and extracted with ether, the ether solution washed with sodium bisulfite solution, sodium carbonate solution and water. Removal of the ether and recrystallization of the residual material from aqueous acetone, alcohol and finally petroleum ether, gave white prisms, m.p. 133.5–134°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.22; H, 6.30.

The flavone is not appreciably soluble in cold, concentrated hydrochloric acid, differing in this respect from 2′,4′,-6′-trimethylflavone, which is appreciably soluble in this acid.

2′,6′-Dimethyl-4′-methoxyflavone hydrogen sulfate was formed when 1.5 ml. of concentrated sulfuric acid was added (dropwise) to a solution of 0.74 g. of the flavone in 35 ml. of dry ether. Removal of the solvent left a solid, which after washing with dry ether and drying was a pale yellow. It gave positive tests for sulfur and sulfate, had m.p. 170.5–171°, and upon titration with standard sodium hydroxide gave values in good agreement with the composition $C_{18}H_{16}O_3 \cdot H_2SO_4$. Upon trituration with water the flavone was reformed.

LOS ANGELES, CALIF.

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[19] D. W. Hill and R. R. Melhuish, *J. Chem. Soc.*, 1165 (1935).

[20] L. Gattermann, *Ann.*, **357**, 313 (1907).

[21] K. V. Auwers and E. Borsche, *Ber.*, **48**, 1714 (1915).

[22] First prepared by J. W. Bolger, in unpublished experiments in this Laboratory.

[23] W. N. Nagai, *Ber.*, **25**, 1288 (1892).

[24] A. Zaki and R. C. Azzam, *J. Chem. Soc.*, 434 (1943).