The Oxidation of Flavonols by Periodic Acid[1]

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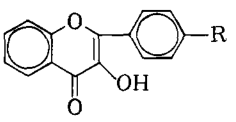
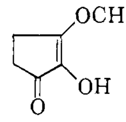
Received August 14, 1962

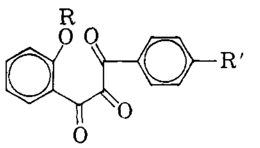
Flavonol (Ia) and 4′-methoxyflavonol (Ib) consume one mole of periodate per mole of compound,[2] and neutral products containing one more oxygen atom than the flavonol have been isolated. Spectral and chemical data indicate that these products are 2-aroyl-2-hydroxy-3(2*H*)-benzofuranones.

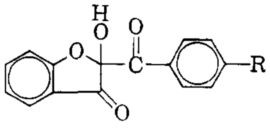
Considering the known reactions of periodic acid, there are three ways in which flavonols might be attacked by periodate: (a) as 1,2-diketones, (b) as analogs of 2-hydroxy-3-methoxy-2-cyclopenten-1-one (II) (reductic acid monomethylether), and (c) as analogs of guaiacol (*o*-methoxyphenol). The results reported have shown that its behavior corresponds to the third possibility and that the products are the 2-aroyl-2-hydroxy-3(2*H*)-benzofuranones Va and Vb.

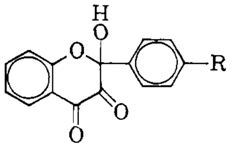
The tautomeric form of a flavonol is a 3,4-flavandione, a 1,2-diketone. It is well known that 1,2-diketones are cleaved by one mole of periodate.[3–5] However, the organic products of such reactions are acids. Since flavonols yield neutral products, it is clear that the relationship to an 1,2-diketone offers no clue to the course of the reaction.

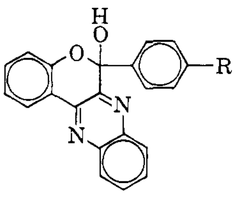

Ia: R = H
Ib: R = OCH_3


II


IIIa: R = R′ = H
IIIb: R = H, R′ = OCH_3
IVa: R = OAc, R′ = H
IVb: R = OAc, R′ = OCH_3


Va: R = H
Vb: R = OCH_3


VIa: R = H
VIb: R = OCH_3


VIIa: R = H
VIIb: R = OCH_3

Hesse and Mix[6] in a study of the behavior of periodic acid toward reductic acid monomethyl ether (II) found that II quickly consumed two moles of periodate and was quantitatively converted to α-ketoglutaric acid. However, the reaction of periodate with the flavonols is quite different in spite of the structural features common to I and II. The flavonols consume only one mole of periodate and yield neutral products.

Apparently flavonol behaves like guaiacol in the reaction. The atoms C-2 and C-3 of the heterocyclic ring of flavonol (Ia) are analogous to the oxygen bearing carbon atoms in guaiacol. That is, they are contiguous atoms, part of an unsaturated system and one of them bears an etherified oxygen, the other a hydroxyl group. Adler[7] has shown that guaiacol reacts with one mole of periodate to form methanol and *o*-quinone, both neutral products.[8]

If the oxidation of the flavonols proceeds in the same way, the reactions should yield the propanetriones IIIa and IIIb. Our studies have shown that these are not the products isolated. The infrared spectra of such compounds should indicate three carbonyl groups and a chelated hydroxyl group. In addition, the products should give strong positive ferric chloride tests. The substances we isolated have none of these properties.

The chemical properties of the flavonol oxidation products lead to some interesting conclusions. In the first place, these products are both reduced by hydrogen iodide in acetic acid, regenerating the original flavonols while liberating a mole of iodine. This demonstrates that the carbon–carbon bonds of flavonol have not been broken. Secondly, the oxidation products react readily with *o*-phenylenediamine to form products having the composition of quinoxalines. This would seem to suggest a 1:2-diketone. Finally, when the oxidation products are acetylated with an acetic anhydride/sodium acetate mixture, the products obtained are the acetates IVa and IVb of the propanetriones IIIa and IIIb.

Since the properties of the oxidation products rule out a propanetrione, the results suggest that we are dealing with an equilibrium mixture of ring chain tautomers. Under these circumstances, one cannot deduce the structure of the crystalline oxidation product from the structure of the derivatives obtained.

The triketones IIIa and IIIb can give rise to two kinds of ring chain tautomers, the 3(2*H*)-benzofuranones Va and Vb and the flavandiones VIa and VIb. When the spectral characteristics of the oxidation products of Ia and Ib are examined, the differences point clearly to the 3(2*H*)-benzofuranone tautomer. The spectral data are tabulated in Table I.

The methoxyl group is known to exert a bathochromic

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[1] Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

[2] M. A. Smith and B. R. Willeford, *Anal. Chem.*, **26**, 751 (1954).

[3] E. L. Jackson, *Org. Reactions*, **2**, 342 (1944).

[4] J. M. Bobbitt, "Advances in Carbohydrate Chemistry," Vol. II, M. L. Wolfrom, ed., Academic Press, Inc., New York, N. Y., 1956, p. 3.

[5] J. R. Dyer, "Methods of Biochemical Analysis," Vol. 3, D. Glick, ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 113.

[6] G. Hesse and H. Mix, *Chem. Ber.*, **92**, 2427 (1959).

[7] E. Adler and R. Magnusson, *Acta Chem. Scand.*, **13**, 505 (1959).

[8] It is quite possible that the first stage of the oxidation of II is analogous to the guaiacol reaction. In both cases, methanol would be liberated. The second mole would then oxidize the triketone to α-ketoglutaric acid. This would not account for the formation of iodine reported by Hesse and Mix.[6]

TABLE I

ABSORPTION MAXIMA FOR THE OXIDATION PRODUCTS OF FLAVONOL AND 4′-METHOXYFLAVONOL

	Solvent	A Product from flavonol	B Product from 4′-methoxyflavonol
λ_{max} (log ϵ)[a]	Ethanol	255 mμ (4.17)	259 m. (4.17)
			290 m. (4.17)
		325 mμ (3.51)	327 m. (3.71)
CO[b]	Carbon tetrachloride	1754 cm.$^{-1}$	1751 cm.$^{-1}$
		1701 cm.$^{-1}$	1686 cm.$^{-1}$
OH[b]	Carbon tetrachloride	3471 cm.$^{-1}$	3413 cm.$^{-1}$

[a] Measured with a Perkin–Elmer Spectracord recording spectrophotometer. [b] Measured with a Perkin–Elmer, Model 21, infrared spectrophotometer equipped with a sodium chloride prism.

effect on the ultraviolet[9] and infrared[10] maxima of carbonyl groups. Such an effect is observed in the oxidation products of Ia and Ib.

There are two carbonyl bands in the infrared spectra of the two oxidation products from the flavonols Ia and Ib. Both products have a high frequency band in the 1755–1750-cm.$^{-1}$ region. Such bands are consistent for the heterocyclic carbonyl of either the benzofuranone or the flavandione formulation. Gripenberg found a carbonyl band at 1730 cm.$^{-1}$ ($CHCl_3$) in 2-hydroxy-2-benzyl-3(2*H*)-benzofuranone[11] and Alder found bands at 1730 and 1760 cm.$^{-1}$ (CCl_4) in rigid bicyclic 1,2-diketones.[12]

The second carbonyl band in the spectra is different for the two oxidation products. In the product from unsubstituted flavonol Ia, the band is at 1701 cm.$^{-1}$. However, if a 4′-methoxyl group is present, this band occurs at 1686 cm.$^{-1}$. Such a bathochromic shift is in accord with expectations if one assigns these low frequency bands to the carbonyl of the 2-aroyl substituents of the 3(2*H*)-benzofuranones Va and Vb. On the other hand, both carbonyl groups in the flavandione formulations VIa and VIb are "isolated" from the methoxyl group by the sp^3 carbon at C-2. Hence, no bathochromic shift is to be expected.

An examination of the ultraviolet spectral maxima for the two oxidation products reveals a new strong maximum at 290 mμ when the methoxyl group is present. Presumably, this new band arises from a change in the position and perhaps the intensity of the K band[13] of the carbonyls of the 2-aroyl substituents of the 3(2*H*)-benzofuranones Va and Vb. Such a shift cannot be expected for the flavandiones VIa and VIb.

Finally, the products isolated from the oxidation of the flavonols Ia and Ib are colorless. Leonard and Mader showed that 1,2-diketones are yellow when their carbonyls are coplanar.[14] Models show that the carbonyls in the flavandiones VIa and VIb will be nearly coplanar. One would, therefore, anticipate yellow substances if the oxidation products were flavandiones.

The infrared spectra (CCl_4) of Va and Vb contain sharp bands in the OH region of the spectrum. Since these bands are not affected by dilution, they must arise from intramolecular hydrogen bonding. The spectrum of Va has a band at 3470 cm.$^{-1}$ which is the region assigned by Bellamy[15a] for intramolecular hydrogen bonds (nonchelate). The spectrum of Vb has its hydroxyl band at a lower frequency, namely, 3413 cm.$^{-1}$, which is outside the range set by Bellamy. This lower frequency in the spectrum of the methoxylated product reflects a weaker O—H bond. The effect of the methoxyl on the carbonyl of the 2-aroyl substituent should enhance the hydrogen bonding between this carbonyl and the 2-hydroxyl group and weaken the O—H bond, thus lowering the absorption frequency. Adler has studied the hydroxyl band of methoxylated 2-hydroxylpropiophenones ($CH_3CHOHCOAr$)[16] in carbon tetrachloride. For 4′-hydroxy-3′-methoxy and 3′,4′-dimethoxy compounds sharp bands were found at 3540 and 3500 cm.$^{-1}$ (CCl_4), respectively.

The reaction between the oxidation products and *o*-phenylenediamine take place readily in chloroform.[17] It is known that 2-hydroxy-3(2*H*)-benzofuranones will react with *o*-phenylenediamine to form quinoxalines.[18] In this case the liberated phenolic hydroxyls appear to form the hemiketals VIIa and VIIb, for the spectra (potassium bromide pellet) show no bands in the carbonyl region. In the hydroxyl region, the spectrum of the quinoxaline from the flavonol product contained a broad band between 3000 and 3300 cm.$^{-1}$, while the spectrum of the methoxyl containing analog had a rather sharp band at 3380 cm.$^{-1}$.

Both oxidation products yielded monoacetyl derivatives. The infrared spectra of both products indicated that the reaction had taken place with ring opening and that the products were the acetates of the diphenylpropanetriones IVa and IVb. Both spectra (CCl_4) contained carbonyl bands between 1780 and 1790 cm.,$^{-1}$ the range normally assigned to phenyl esters.[15b] Each spectrum had three additional bands in the carbonyl region and neither compound absorbed in the hydroxyl region. To the best of our knowledge, diphenyl propanetriones with an ortho hydroxyl group are unknown. Gramshaw, Johnson, and King[19] oxidized a methoxylated 2-flavene with osmium tetraoxide and reported a small yield of such a trione. However, the spectra of their product and ours were quite different.

When an acetic acid solution of either oxidation product is mixed with concentrated hydrogen iodide, and allowed to stand at room temperature, the reaction mixture darkens due to the liberation of iodine. In addition, crystals of the original flavonol are formed.

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(9) Numerous relevant examples may be found in such references as M. J. Kamlet, ed., "Organic Electronic Spectra," Vol. 1, Interscience Publishers, New York, N. Y., 1960, pp. 1946–1952; and L. Lang, "Absorption Spectra in the Ultraviolet and Visible Regions," Academic Press, New York, N. Y., 1961.

(10) In flavanones, B. L. Shaw and T. H. Simpson, *J. Chem. Soc.*, 655 (1955); in 3(2*H*)-benzofuranones, C. Eneback and J. Gripenberg, *Acta Chem. Scand.*, **11**, 871 (1957); in acetophenones, M. Yamaguchi, *J. Chem. Soc. Japan*, **78**, 1240 (1957); N. Fuson, M.-L. Josien and E. M. Shelton, *J. Am. Chem. Soc.*, **76**, 2526 (1954).

(11) C. Eneback and J. Gripenberg, *Acta Chem. Scand.*, **11**, 871 (1957).

(12) K. Alder, H. K. Schafer, H. Esser, H. Krieger and R. Reubke, *Ann.*, **593**, 23 (1955).

(13) A. F. Gillam and E. S. Stern, "An Introduction to Electronic Spectroscopy in Organic Chemistry," Edward Arnold, Ltd., London, 1957, Chap. 8.

(14) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).

(15) L. J. Belamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958; (a) p. 96; (b) p. 182.

(16) E. Adler, private communication.

(17) E. Adler, L. Junghahn, V. Lindberg, B. Berggren, and G. Westin, *Acta Chem. Scand.*, **14**, 1261 (1960).

(18) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953, p. 296.

(19) J. W. Gramshaw, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4040 (1958).

The reaction appears to be quantitative (see Experimental) and must involve an opening of the ring and reduction.

Experimental

Spectra.—Ultraviolet spectra were measured with a Perkin–Elmer Spectracord using 1-cm. quartz cells. Infrared spectra were, with one exception, measured with a Perkin–Elmer, Model 21, spectrophotometer equipped with a sodium chloride prism. The exception is the acetate of the oxidation product of 4′-methoxyflavonol (see below).

Oxidation of Flavonol with Periodic Acid.—Flavonol (10.4 g., 43.7 mmoles) was dissolved in 500 ml. of purified[20] dioxane, freshly distilled from sodium. A solution of periodic acid (11.2 g., H_5IO_6, 49 mmoles) in 500 ml. of water was slowly (5 min.) added to the stirred dioxane solution of flavonol. The flavonol began to precipitate about half way through the addition but redissolved to yield a clear deep red solution after 20 min. At the end of 30 min., the reaction mixture was added to a solution of sodium bisulfite (30 g., 580 meq.) and sulfuric acid (10 ml. of 1 *M* H_2SO_4) in 100 ml. of water. A clear yellow solution was obtained. The solvents were removed *in vacuo* on a film evaporator. The residue consisted of a heavy oil and an aqueous layer. The oil was extracted with three portions (200, 2 × 100 ml.) of ether. The ether layer was washed with 100 ml. of saturated sodium bicarbonate and dried over calcium sulfate. Evaporation of the ether yielded 10 g. of a heavy oil. This dissolved in 20 ml. of methylene chloride to which 50 ml. of hexane then was added. Upon standing in the ice box, 6.92 g. of large crystals appeared which were collected. The addition of more hexane yielded an additional 1.07 g. of colorless crystals. The combined yielded of these two crops of **2-hydroxy-2-benzoyl-3(2*H*)-benzofuranone (Va)** was 75%. The melting point of Va is not sharp. It begins to soften at about 90°, appearing to melt between 95 and 97°. The spectral properties of Va are listed in Table I, column A, and discussed in the text. The product Va decolorized permanganate but gave no color with ferric chloride. It did not dissolve in 5% sodium bicarbonate but yielded a deep yellow solution with 5% sodium hydroxide.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.85; H, 3.94; mol. wt., 254. Found: C, 71.19; H, 4.15; mol. wt., 241 (Rast).

Reaction of Va with *o*-Phenylenediamine.—The procedure followed was that of Adler and co-workers.[17] Chloroform (25 ml.) was used as a solvent for the benzofuranone (100 mg., 0.49 mmole) and the *o*-phenylenediamine (53 mg., 0.49 mmole). After standing overnight in the presence of anhydrous sodium sulfate, the reaction mixture was filtered, extracted with dilute sulfuric acid (1 *M*) followed by saturated sodium bicarbonate. After drying ($CaSO_4$), evaporation of the solvent yielded 114 mg. (88%) of a yellow solid which was recrystallized from methylene chloride (15 ml.); yellow needles, m.p. 237–238°.

Anal. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.29; N, 8.59. Found: C, 77.91; H, 4.22; N, 9.24.

Acetylation of Va.—A mixture of acetic anhydride (10 ml.), sodium acetate (0.50 g.) and Va (0.50 g.) was refluxed for 2 hr. The hot solution was poured into water; the resulting solid was collected and recrystallized twice from ethanol affording light orange crystals of 1-(*o*-acetoxyphenyl)-3-phenylpropanetrione (IVa), m.p. 128–129°. Infrared bands (CCl_4), 1792 (arylacetate), 1761, 1745, 1709 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.91; H, 408; Ac, 14.53; CH_3C-, 9.13; mol. wt., 296. Found: C, 68.78, 67.98; H, 4.24, 3.99; Ac, 28.72; CH_3C-, 9.35; mol. wt., 298.

The anomalous acetyl value probably arises from the analytical procedure. Diphenylpropanetrione yields carbonate ion with alkali[21] and this would appear as carbon dioxide during the distillation of the acetic acid and be titrated with the acetic acid as a monobasic acid.

Reduction of Va with Hydrogen Iodide in Acetic Acid.—Freshly distilled, colorless hydrogen iodide was used. From 50 to 100 mg. of Va was dissolved in 1 ml. of acetic acid. Soon after the addition of 1 ml. of hydriodic acid, the mixture set to a pasty mass, presumably a mixture of iodine and flavonol. The addition of a little alcohol served to dissolve the iodine and the flavonol was collected by filtration. The filtrate was titrated with thiosulfate. Moles of I_2, 0.985, 0.973; moles of flavonol, 0.83, 0.76.

Oxidation of 4-Methoxyflavonol with Periodic Acid.—The oxidation was carried out much as described above for flavonol. The methoxyflavonol Ib (1.07 g., 4 mmoles) was dissolved in 80 ml. of purified dioxane[20] and mixed with a solution of periodic acid (1.14 g., H_5IO_6, 5 mmoles) in 20 ml. of water. After 20 min., the reaction mixture was worked up as before (5 g. $NaHSO_3$). Evaporation of the ether solution yielded 1.02 g. of a light yellow oil. Recrystallization was effected from 6 ml. of methylene chloride: hexane (2/4, v./v.), 0.54 g. (51%) of crystalline **2-anisoyl-2-hydroxy-3(2*H*)-benzofuranone (Vb)** being obtained. Evaporation of the solvent yielded an 0.30 g. of an oil whose infrared spectrum (neat) indicated that the major component was Vb. The melting behavior of crystalline Vb resembles Va, the range of active melting being 109–112°.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.22; OCH_3, 10.9. Found: C, 67.98, 68.45; H, 4.46, 4.58; OCH_3, 10.40.

Reaction of Vb with *o*-Phenylenediamine.—This reaction was carried out as above for Va and the quinoxaline recrystallized from ethanol, yellow rods, m.p. 206–207°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 74.14; H, 4.45; N, 7.87; OCH_3, 8.71. Found: C, 74.63, 74.42; H, 4.75, 4.75; N, 7.71; OCH_3, 8.86.

Acetylation of Vb.—The reaction was carried out as described for Va (0.5 g. of Vb) above except that the gummy product was dissolved in ether (60 ml.) and the ether solution extracted with sodium bicarbonate and dried over sodium sulfate. Evaporation of the ether left a 49% yield of 1-anisoyl-3-(*o*-acetoxyphenyl)-propanetrione (IVb). Recrystallization from ethanol afforded light reddish crystals, m.p. 115.5–116.5°. Infrared bands (CCl_4) 1790 cm.$^{-1}$ (arylacetate), 1760, 1745, 1705 cm.$^{-1}$.[22]

Anal. Calcd. for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32; OCH_3, 9.51. Found: C, 66.43; H, 4.54; OCH_3, 9.39.

Reaction of Vb with Hydrogen Iodide in Acetic Acid.—The reaction was carried out as described for Va above. The reaction was somewhat slower and the results less quantitative. Moles of I_2: 0.71, 0.50, 0.60; moles of 4′-methoxyflavonol, 0.71, 0.87, 0.54.

Acknowledgment.—The author wishes to acknowledge the generosity of the National Science Foundation for a Science Faculty Fellowship as well as the kindness of Professor E. Adler of the Institute of Organic Chemistry, Chalmers Tekniska Hogskola, Gothenberg, Sweden, in providing laboratory facilities where much of this work was carried out. In addition to many helpful discussions with Professor Adler, the author also wishes to acknowledge the help of Dr. W. D. Ollis of the University of Bristol in interpreting some of the spectral data.

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(20) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath, Boston, Mass., 1957, p. 285. C.P. dioxane, freshly distilled from sodium, has been used with only a minor decrease in yield.

(21) J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 618 (1951).

(22) Measured in CCl_4 solution (40 mg./10 ml.) using a Perkin–Elmer, Model 137 Infracord, sodium chloride prism. Values rounded off to the nearest 5 cm.$^{-1}$.