The Oxidation of Flavonols by Periodic Acid in Methanol

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The oxidation of flavonols by periodic acid in methanol gives rise to derivatives of 2-methoxy-3,4-flavandione. The infrared spectra of these compounds are reported and interpreted.

It has been shown that flavonols (I) are oxidized by periodic acid in aqueous dioxane to form 3(2H)-benzofuranones II,[2] a ring–chain tautomer of the hydroxypropanetrione III, and the flavandione IV. Derivatives of both III and IV have been prepared (*i.e.*, V and VI).

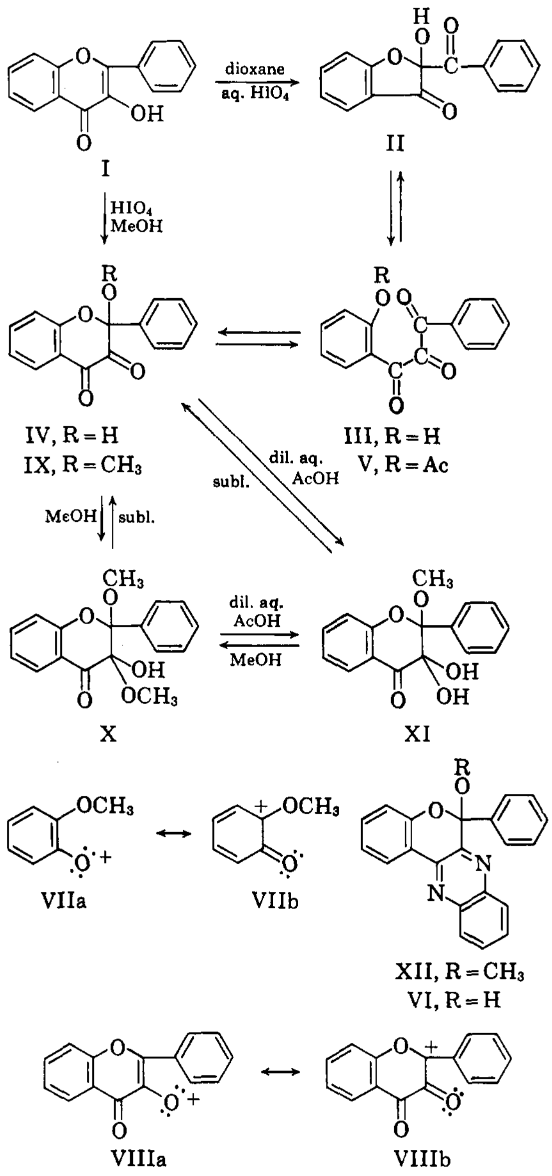
The reaction between flavonols and periodate is analogous to that between guaiacols and periodate. Adler and Magnusson[3] have shown that guiaicols are converted to *o*-quinones. Adler, Falkehag, and Smith have proposed a mechanism[4] in which the oxidant generates a cation, two of whose resonance contributors are shown as VIIa and VIIb. When the same mechanism is applied to the flavonol, the resonance hybride of the corresponding cation can be represented by VIIIa and VIIIb. Paralleling Adler's oxidation mechanism for guaiacol, one can account for the formation of the benzofuranone II in aqueous dioxane. The cation (VIIIa,b) is attacked by water at C-2 to form the hemiketal IV which then rearranges to form the more stable benzofuranone II.

When the oxidation of flavonol (I) is carried out in methanol the product formed is X, a 3-heimiketal of the 3,4-flavandione IX (see Scheme I).[5] The formation of such a product is readily accommodated by the Adler oxidation mechanism. When methanol is present, it attacks the cation (VIIIa,b) at C-2 forming IX, a ketal, which, unlike the hemiketal IV, cannot undergo ring–chain tautomerism. The actual product isolated is the colorless methyl 3-heimiketal, X. Sublimation converts X to the flavandione IX and recrystallization from dilute acetic acid yields the hydrate XI. All three compounds, IX, X, and XI, react with *o*-phenylenediamine to form the same quinoxaline, XII. They are all reduced to flavonol by hydriodic acid, a property they share with the benzofuranones (II).

The reaction has been extended to three additional methoxyflavonols, 4′-methoxyflavonol, 7-methoxyflavonol, and 4′,7-dimethoxyflavonol. In each case, a family of compounds analogous to IX, X, XI, and XII was isolated and characterized. The spectral properties of the first three of these compounds are reported in Table I.

The flavandiones have two bands in the carbonyl region, one near 1700, the other near 1770 cm.$^{-1}$ (CCl_4). The lower of these two frequencies can be attributed to the aryl carbonyl at C-4. This assignment is supported by the bathochromic shift of 10 cm.$^{-1}$ when a 7-OCH_3 is present (compounds IX and XIII *vs.* XVI and XIX). The higher frequency band must be due to the carbonyl at C-3. Alder and co-workers[6] have shown that the spectra of α-diketones have high frequency carbonyl bands when the carbonyls are *cis* and coplanar. Thus, camphorquinone has bands at 1760 and 1776 cm.$^{-1}$ (CCl_4).

Scheme I



It is hardly surprising that the C-3 carbonyls of the diones, flanked as they are by C-2 and C-4, each with strong electron-withdrawing groups, form stable hemiketals and hydrates. An analogy exists in the well-known hydrate of 1,3-diphenylpropanetrione.

A consideration of the geometry of the hemiketals and hydrates has led us to an interpretation of the hydroxyl bands found in the infrared spectra of these

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[1] This work formed part of the M.S. Thesis of R.A.W.

[2] M. A. Smith, *J. Org. Chem.*, **28**, 933 (1963).

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

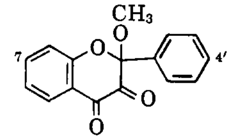
[4] E. Adler, I. Falkehag, and B. Smith, *ibid.*, **16**, 529 (1962).

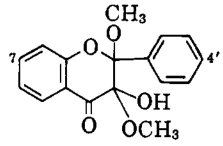
[5] Dr. Hans-Dieter Becker has recently prepared the same hemiketal from a dimerization product of flavonol: see *J. Org. Chem.*, **30**, 989 (1965).

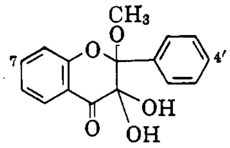
[6] K. Alder, H. K. Schafer, H. Esser, H. Krieger, and R. Reubke, *Ann.*, **593**, 23 (1953).

TABLE I

INFRARED BANDS OF RELATED 2-METHOXY-3,4-FLAVANDIONES AND DERIVATIVES

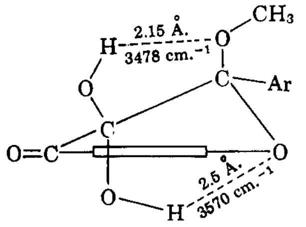






	Dione		Dione 3-hemiketal			Dione 3-hydrate		
Substituents	Compd.	ν_{CO}, cm.$^{-1}$	Compd.	ν_{CO}, cm.$^{-1}$	ν_{OH}, cm.$^{-1}$	Compd.	ν_{CO}, cm.$^{-1}$	ν_{OH}, cm.$^{-1}$
None	IX	1703 1768	X	1705	3485	XI	1715	3475 3570
4'-OCH$_3$	XIII	1702 1768	XIV	1703	3490	XV	1715	3480 3570
7-OCH$_3$	XVI	1692 1768	XVII	1690	3475	XVIII	1706	3470 3570
7,4'-(OCH$_3$)$_2$	XIX	1692 1767	XX	1690	3480	XXI	1703	3470 3570

compounds (see Table I). Dilution studies (0.05 *M* to 0.01 *M*) revealed no change in either the position or the intensity of these bands so that both classes of molecules have intramolecular hydrogen bridging.[7] The data suggest that these hydrogen bridges involve the oxygen of the 2-methoxy group and the oxygen of the heterocyclic ring. We have assumed the half-chair conformation (A) with the bulky aryl group at C-2 in an equatorial position.[8] Dreiding models of such a structure show that the equatorial hydroxyl at C-3 can approach to within 2.15 Å. of the axial methoxyl at C-2. The band at 3478 cm.$^{-1}$ is attributed to this structural feature. This band is also present in the hemiketal. The hydrate has a second band at a higher frequency, 3570 cm.$^{-1}$. We have assigned this band to a hydrogen bridge between the axial C-3 hydroxyl and the heterocyclic oxygen of the ring. Dreiding models indicate 2.5 Å. as the minimum distance between these two atoms so that it is a weaker hydrogen bridge than the one previously discussed. It is not surprising that this weaker hydrogen bridge is the one which disappears on formation of the hemiketal.



A

There is an alternate site for hydrogen bridges, namely, to the electrons of the aryl ring on C-2 which is β to the hydroxyls. Schleyer, Winter, Trifan, and Bacskai[9] inferred such an intramolecular hydrogen bridge from the infrared spectra (CCl$_4$) of β-phenylethanols. They attributed a band at about 3600 cm.$^{-1}$ to a hydrogen bridge between the alcoholic hydroxyl and the aryl ring. The higher frequency band at 3570 cm.$^{-1}$ in the hydrates (Table I: XI, XV, XVIII, and XXI) is close enough to 3600 cm.$^{-1}$ to warrant consideration. We are inclined to believe that this band at 3570 cm.$^{-1}$ is too low to be attributed to an H-bridge to the aryl group. The lowest band reported by Schleyer, *et al.*, 3595 cm.$^{-1}$, is for β-(*p*-dimethylaminophenyl)ethanol. The *p*-methoxy analog absorbs at 3602 cm.$^{-1}$ while β-phenylethanol itself has the band at 3604 cm.$^{-1}$.

It will be observed that both the hydrate and the hemiketal have a carbonyl at C-4. As shown by the data in Table I the frequency of the carbonyl stretching band is 10–15 cm.$^{-1}$ higher in the hydrate in all cases. This is probably a reflection of the greater ring strain arising from the second hydrogen bridge in the hydrate. In discussing the spectra of the diones it was noted that a 7-methoxy group resulted in a bathochromic shift of about 10 cm.$^{-1}$ in the C-4 carbonyl band. Such an effect is also present in the hydrates and the hemiketals (Table I).

Experimental

The flavonols were prepared by condensation of the appropriate benzaldehyde and *o*-hydroxyacetophenone in the presence of base followed by hydrogen peroxide. The intermediate chalcones were not isolated.[10]

All infrared spectra were run in carbon tetrachloride using a Beckman IR-8 spectrophotometer (grating). On each spectrum, polystyrene bands at 3026 and 1603 cm.$^{-1}$ were also recorded and appropriate corrections made if the location of these bands was not correct.

The melting points are uncorrected. It will be noted that the hemiketals and the hydrates melt over a range. The melting takes place with the evolution of a gas and the development of a yellow color. Presumably this is due to their decomposition into methanol or water and the dione.

2-Methoxy-3,4-flavandione Methyl 3-Hemiketal (X).—A mixture of 10 g. (42 mmoles) of flavonol (I), 12 g. (53 mmoles) of periodic acid (H_5IO_6), and 1 l. of methanol was stirred for 30 min. The suspended flavonol slowly dissolved and a clear red solution resulted. There was a temperature rise of a few degrees. The oxidant was removed by passing the mixture through a bed of IRA 400 Amberlite resin (acetate form[11]), a process which changed the deep red color to yellow. Crystals of X separated when the solution was evaporated *in vacuo* to 25–50 ml. The yield was 5.1 g. (17 mmoles), m.p. 151–152° dec. Further concentration yielded 0.30 g. of X, m.p. 150–151° dec. The combined yield was 43%.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; OCH$_3$ 20.7. Found: C, 67.99; H, 5.10; OCH$_3$, 21.9, 22.3.

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[7] G. C. Pimentel, A. L. McClellan, "The Hydrogen Bond," W. H. Freeman Co., San Francisco, Calif., 1960, p. 175.

[8] W. B. Whalley, "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., The Macmillan Co., New York, N. Y., 1962, p. 449.

[9] P. R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, **No. 14**, 1 (1959).

[10] M. A. Smith and R. M. Neumann, unpublished results.

[11] A satisfactory resin can be prepared by mixing 600 g. of the chloride form of the resin with 2 l. of 3 *M* sodium acetate, decanting, washing with water, and repeating the process once.

2-Methoxy-3,4-flavandione 3-Hydrate (XI).—The methyl 3-hemiketal (X) of 2-methoxy-3,4-flavandione (0.50 g., 1.67 mmoles) was distilled with toluene until 100 ml. of distillate had been collected. The rest of the solvent was then removed and the residual oil was crystallized from 13 ml. of 50% (v./v.) aqueous acetic acid. The product (XI) separated as white crystals (0.38 g., 80%). A second recrystallization from the same solvent yielded a product melting at 159–161°. It was also possible to prepare XI directly from X by recrystallization from 50% aqueous acetic acid.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93; OCH_3, 10.84; mol. wt., 286. Found: C, 67.24; H, 5.05; OCH_3, 10.49; mol. wt., 277.

2-Methoxy-3,4-flavandione (IX).—This dione was prepared from the hemiketal (X) by sublimation *in vacuo* using the apparatus designed by Mallory.[12] At about 0.5 mm., an oil-bath temperature of 180–200° was sufficient. After several sublimations, a yellow solid, melting at 109.5–111°, was obtained.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51; OCH_3, 11.57. Found: C, 71.85; H, 4.30; OCH_3, 12.17, 12.36.

2-Methoxy-3,4-flavandione Quinoxaline (XII).—A solution of 0.50 g. (1.67 mmoles) of X and 0.18 g. (1.67 mmoles) of *o*-phenylenediamine in 100 ml. of $CHCl_3$ was refluxed 2 days with 8 g. of anhydrous $MgSO_4$. The drying agent was removed and the resulting solution was extracted with three 20-ml. portions of 1 *M* H_2SO_4 and three 20-ml. portions of saturated $NaHCO_3$. The resulting pale yellow solution was filtered, dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness. Crystallization of the resulting white solid was effected with 20 ml. of 95% EtOH. The yield was 0.38 g. (67%) of white needles, m.p. 169–170°.

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23; OCH_3, 9.12. Found: C, 77.91; H, 4.59; N, 8.32; OCH_3, 9.00.

A similar reaction carried out with the hydrate XI and the dione IX yielded the same product (by mixture melting point and infrared spectra).

2,4′-Dimethoxy-3,4-flavandione Methyl 3-Hemiketal (XIV).—This product was prepared from 4′-methoxyflavonol by the same procedure which converted I to X. The product (43%) was in the form of white needles, m.p. 162–164°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49; OCH_3, 28.43. Found: C, 65.38; H, 5.60; OCH_3, 27.80.

2,4′-Dimethoxy-3,4-flavandione 3-Hydrate (XV).—This product was prepared from XIV by the same procedure which converted X to XI. The product was in the form of pale yellow needles, m.p. 163–165°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10; OCH_3, 19.62. Found: C, 64.68; H, 5.01; OCH_3, 19.42.

2,4′-Dimethoxy-3,4-flavandione (XIII).—This product was prepared from XIV by vacuum sublimation. The product was a dark yellow solid, m.p. 124–126°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73; OCH_3, 20.81. Found: C, 68.36; H, 4.91; OCH_3, 21.37, 21.13.

2,4′-Dimethoxy-3,4-flavandione Quinoxaline.—This product was prepared from XIV by the same procedure which converted X to XII. The product (87%) was in the form of white needles, m.p. 166–167° (95% EtOH).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.59; H, 4.90; N, 7.56; OCH_3, 16.76. Found: C, 74.58; H, 4.74; N, 7.82; OCH_3, 16.59.

A similar reaction carried out with the hydrate XV and the dione XIII yielded the same product (identified by mixture melting point and infrared spectra).

2,7-Dimethoxy-3,4-flavandione Methyl 3-Hemiketal (XVII).—This product was prepared from 7-methoxyflavonol by the same procedure which converted I to X. The product (35%) was in the form of white needles, m.p. 142–144.5° (MeOH).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49; OCH_3, 28.43. Found: C, 65.32; H, 5.44; OCH_3, 27.98.

2,7-Dimethoxy-3,4-flavandione 3-Hydrate (XVIII).—This product was prepared from XVII by the same procedure which converted X to XI. The product was in the form of white needles, m.p. 148–150°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.57; H, 5.10; OCH_3, 19.63. Found: C, 64.37; H, 5.13; OCH_3, 18.87.

2,7-Dimethoxy-3,4-flavandione (XVI).—This product was prepared from XVII by vacuum sublimation. The yellow solid melted at 129–131°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73; OCH_3, 20.85. Found: C, 68.27; H, 4.96; OCH_3, 20.80.

2,7,4′-Trimethoxy-3,4-flavandione Methyl 3-Hemiketal (XX).—This product was prepared from 7,4′-dimethoxyflavonol by the same procedure which converted I to X. The product (59%) was obtained as white needles, m.p. 169–172° (MeOH).

Anal. Calcd. for $C_{19}H_{20}O_7$: C, 63.32; H, 5.59; OCH_3, 34.45; mol. wt., 360. Found: C, 63.40; H, 5.62; OCH_3, 35.53; mol. wt., 356.

2,7,4′-Trimethoxy-3,4-flavandione 3-Hydrate (XXI).—This product was prepared from XX by the same procedure which converted X to XI. The product was in the form of white needles, m.p. 149–51°.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.43; H, 5.24; OCH_3, 26.88. Found: C, 62.39; H, 5.15; OCH_3, 26.06.

2,7,4′-Trimethoxy-3,4-flavandione (XIX).—This product was prepared from XX by vacuum sublimation. The yellow solid melted at 157–159°.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91; OCH_3, 28.36. Found: C, 65.48; H, 5.70; OCH_3, 27.95.

2,7,4′-Trimethoxy-3,4-flavandione Quinoxaline.—This product was prepared from XX by the same procedure which converted X to XII. The product (90%) was in the form of pale yellow needles, m.p. 221–222° (95% EtOH).

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00; OCH_3, 23.25. Found: C, 72.48; H, 5.34; N, 6.85; OCH_3, 23.12.

A similar reaction, carried out with the hydrate XXI and the dione XIX, yielded the same product (by mixture melting point and infrared spectra).

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[12] F. B. Mallory, *J. Chem. Ed.*, **39**, 261 (1962); available (No. K-85500) from Kontes Glass Co., Vineland, N. J.