Nuclear Bishydroxylation with Peroxydisulfate

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Oxidation of 3,3′,4′,7-tetra-*O*-methylquercetin by alkaline peroxydisulfate gave, in addition to the known 5,8-dihydroxy derivative, a comparable yield of the 5,6,8-trihydroxy compound. It was characterized by complete methylation and by conversion to the corresponding hydroxy and methoxy flavoquinones. Simultaneous introduction of two hydroxyls *o*- and *p*- to an existing hydroxyl function can be a potential step-saver in the synthesis of polyphenolic substances.

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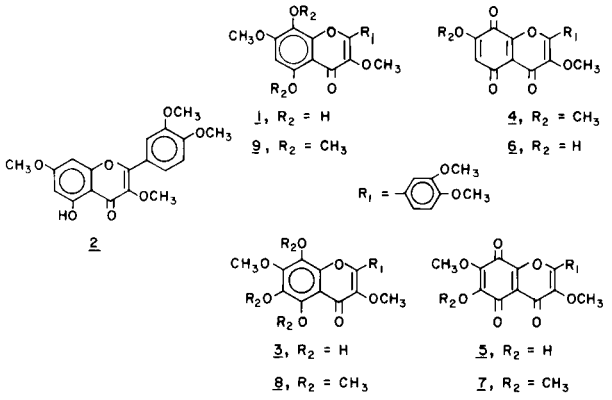
One of the significant steps in the synthesis of flavonoid compounds was the application of "Elb's persulfate-oxidation" for hydroxylation of the position para to the existing hydroxyl (2,3,4). Synthesis of a large number of polyhydroxyflavones, isoflavones, chalcones, xanthones, *etc.*, was simplified through the application of this "nuclear oxidation step" to appropriately substituted intermediates (5). Continued interest in this reaction is reflected by a recent publication in which Cu^{++} catalyzed hydroxylation by this reagent under acid conditions was described (6). We had an occasion to prepare 5,8-dihydroxy-3,3′,4′,7-tetramethoxyflavone (**1**) by the oxidation of 5-hydroxy-3,3′,4′,7-tetramethoxyflavone (**2**) (3). Careful processing of the reaction mixture gave, in addition to the expected **1**, a second product, characterized as 5,6,8-trihydroxy-2,3′,4′,7-tetramethoxyflavone (**3**). This paper describes the characterization of **3** and details and significane of the reaction .



Oxidation of **2** with 1-2 equivalents of peroxydisulfate as described in the literature (3), followed by oxidation of the product with ferric nitrate, or preferably, tetrachloro-*o*-quinone gave a mixture of two flavoquinones. These were readily separable by partition between chloroform and aqueous sodium bicarbonate. The neutral quinone **4** was the expected gossypetone tetramethyl ether (3). The acidic quinone was recovered as an orange red crystalline solid with spectral properties similar to those of **4**. On the premise that demethylation of the 7-methoxyl function could have occurred during the oxidation (7), resulting in the formation of a compound such as **6**, the acidic quinone was subjected to methylation with diazomethane. The product was different from **4**. Its correct structure as **7** was deduced from a comparison of its nmr spectrum with that of **4**. The spectra were nearly identical except that **7** had five methoxyls instead of four and lacked a one-proton signal at τ 3.50, assigned to H_6.

The acidic quinone **5** on reduction gave the pure trihydroxy compound **3** which was present in the original oxidation product but was difficult to separate because of the similar solubility characteristics to those of **1** and tendency towards oxidation. Since oxidation to the quinone mixture was nearly quantitative and separation of the quinones could be accomplished readily, this method of separation was practical.

Methylation of **3** gave **8** which was shown to be identical with the known 3,3′,4′,5,6,7,8-heptamethoxyflavone (8). Thus, oxidation of **2** by alkaline peroxydisulfate gave a mixture of the dihydroxy **1** and the trihydroxy **3** flavones.

In order to ascertain this, the purity and homogeneity

Table 1

Yields of **1** and **3** During Oxidation with Peroxydisulfate

Moles of **2**	Moles of KOH	Moles of $K_2S_2O_8$	Composition of the Product **1**	**3**
1	10	1	64	36
1	10	2	55	45
1	10	3	55	45
1	10	3	50	50

of the starting materials was reestablished before oxidation. The quercetin, obtained by hydrolysis of commercial rutin was homogeneous (paper chromatography in three systems). Since partial methylation of quercetin can lead to a number of intermediates (9) a carefully purified sample of **1** was prepared (tlc, m.p., nmr and mass-spectrum) and subjected to oxidation with the same result.

Next, the effect of varying amounts of oxidant on the composition of the product mixture was studied by complete methylation of the oxidation products, followed by quantitative tlc of **8** and **9**. The results (Table 1) showed that although **1** was the major product, **3** was formed in substantial yield also. This is a significant result because bishydroxylation has not been reported in the extensive literature on the oxidation of flavonoid compounds (5). A number of papers appeared in which *ortho*-hydroxylation was forced by substituents at the para position but the yields were low (10,11). Concurrent hydroxylation to form quinol and catechol derivatives was observed in which the ratio of the two products varied from 6:1 to 22:1 (12). Studies described here show that it is possible to hydroxylate both positions of the aromatic ring simultaneously and in practical yields. The method will be of potential value in the synthesis of certain polyhydroxy anthraquinones, xanthones and flavonoid compounds.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and were uncorrected. The following instruments were used for the spectra recorded: Beckman DB (uv), Beckman-Acculab-3 (ir), Varian A60A with tetramethylsilane as internal standard (nmr) and Hitachi-Perkin-Elmer RMU-6E (mass spectra). The thin-layer chromatography was performed using silica gel Merck-HF 254+366.

Oxidation.

This is an improvement of published procedure (3) and gives relatively pure products. To a solution of tetra-*O*-methylquercetin (**2**, 1.08 g., 3 mmoles) in pyridine (20 ml.) and 2*N* potassium hydroxide (10 ml.) was added, dropwise, aqueous potassium peroxydisulfate (1.6 g., 6 mmoles in 60 ml.) over 2 hours at 20°. After 24 hours, the dark reaction mixture was concentrated to 20 ml. to remove most of the pyridine. After removal of the unreacted starting material (0.2 g.) by extraction with chloroform the aqueous layer was extracted twice with equal volumes of 4:1 phenol-chloroform. The combined extract was shaken with water (25 ml.) and isopropyl ether (100 ml.). The aqueous layer was washed once more with isopropyl ether (30 ml.) and acidified to 0.2*N* hydrochloric acid. It was then heated at 100° for 30 minutes, cooled and the solid filtered, yield, 0.45 g. (55%). It was a mixture of **1** and **3**.

Oxidation to Flavoquinones **4** and **5**.

The above mixture of **1** and **3** (1 g.) was dissolved in 20% of methanol in chloroform (100 ml.) and treated with a solution of tetrachloro-*o*-quinone (0.67 g.) in chloroform (10 ml.). After 10 minutes, the reaction mixture was concentrated to a small volume and the crystalline solid filtered and washed with methanol-ether (1:3). It was taken up in chloroform (30 ml.) and washed twice with 5% aqueous sodium bicarbonate (10 ml. each). The solvent layer was separated, dried (sodium sulfate) and concentrated to dryness. The solid was crystallized from methanol-chloroform to give brick-red needles of **4**, m.p. 254-257°; yield, 0.45 g. (lit. m.p. 254-257°) (3).

The purple aqueous layer was acidified and extracted with chloroform. Concentration of the solvent layer gave a solid which was crystallized from methanol to give orange red needles of **5**, m.p. 252-254°, yield, 0.4 g.

Anal. Calcd. for $C_{19}H_{16}O_9$: C, 58.76; H, 4.15. Found: C, 58.61; H, 4.15.

3,3′,4′,6,7-Pentamethoxyflavoquinone (**7**).

A solution of **5** (0.1 g.) in chloroform (10 ml.) was treated with a slight excess of diazomethane. When an aliquot gave no purple color with aqueous bicarbonate, the solvent layer was concentrated to dryness. The solid separated from methanol as orange-red needles, m.p. 211-212°

Anal. Calcd. for $C_{20}H_{18}O_9$: C, 59,70; H, 4.51. Found: C, 59.50; H, 4.57.

5,6,8-Trihydroxy-3,3′,4′,7-tetramethoxyflavone (**3**).

A sample of **4** (0.1 g.) in methanol (5 ml.) was treated with sodium dithionite (0.1 g.) in water (5 ml.). The yellow solid which separated out was filtered and crystallized from chloroform-methanol, m.p. 262-264°.

Anal. Calcd. for $C_{19}H_{18}O_9$: C, 58.46; H, 4.65. Found: C, 58.64; H, 4.61.

3,3′,4′,5,6,7,8-Heptamethoxyflavone (**8**).

A mixture of **1** and **3** (0.5 g.) in acetone (25 ml.) was boiled under reflux with methyl sulfate (1 ml.) and potassium carbonate (2 g.). After 8 hours, it was concentrated to dryness and the residue dissolved in water (25 ml.). The solid was separated and subjected to chromatography on silicic acid (Mallinkrodt 250-325 mesh) and cellulose (Brown and Co.) mixture (50 g., 1:1), in benzene. Elution with benzene gave a fraction which was obtained as a colorless crystalline solid from methanol, m.p. 129-129° (lit. 128-129°) (8); λ max 342, 270 (inflection) and 254 nm; m/e 432.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.39; H, 5.64.

Further elution of the column with 5% acetone in benzene gave the second band which on concentration and crystallization from methanol gave **9**, m.p. 170-172° (lit. 170-172°) (3).

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