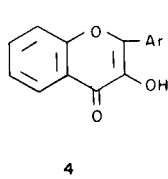
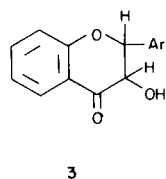
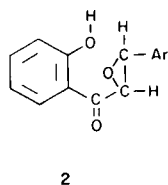
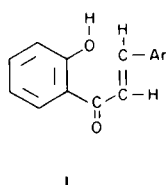


A Modification of the Algar-Flynn-Oyamada Preparation of Flavonols

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Flavonols (**4**) are readily prepared from 2'-hydroxychalcones (**1**) and alkaline hydrogen peroxide. This widely used method is now referred to as the Algar-Flynn-Oyamada (AFO) reaction in the literature (1-4). We report here a modification of the AFO reaction in which the starting materials are *o*-hydroxyacetophenone and an aldehyde, the intermediate 2'-hydroxychalcone being oxidized *in situ*. In order to demonstrate the generality of this procedure, we extended the reaction to include several flavonols, one of which is a new compound. In the course of a literature search on 3',4'-methylenedioxyflavonol, we learned that Ozawa and coworkers (5) had developed a very similar procedure. Since Ozawa's procedure has not been mentioned in the AFO surveys available to us (1-4), we decided to publish our later results to widen the usage of the procedure.



It has been shown that 3-hydroxyflavanones (**3**) are intermediates in this reaction and it has been assumed that a ketoepoxide (**2**) is a precursor of **3**. This mechanism has been challenged by Dean (6) who presents evidence that ketoepoxides are not intermediates.

In most cases, the chalcone is prepared from the appropriate *o*-hydroxyacetophenone and a benzaldehyde

by condensation with sodium or potassium hydroxide in an alcoholic solution. The literature records several attempts to prepare the flavonol directly from the hydroxyacetophenone and the aldehyde. Marathey (7) reported success (30-40 mole percent yield) in using sodium peroxide directly on the mixture of ketone and aldehyde. Gowan, Hayden and Wheeler (8) condensed α -chloroacetophenone with the aldehyde in an excess of cold alkali and obtained up to 35 percent yields of the flavonol. In the Rasoda or Ranjorwa reaction (9) the ketone and the aldehyde are slowly oxidized by air in the presence of 10N sodium hydroxide.

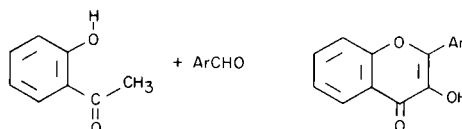
However, in the usual AFO procedure, the chalcone is isolated and then oxidized with alkaline hydrogen peroxide. Since the chalcone is formed under alkaline conditions, it occurred to us to by-pass the isolation of the chalcone and add the peroxide directly to the sodium salt of the chalcone. As indicated in Table I, this procedure was reasonably successful, resulting in flavonol yields of 40-60 percent.

Attempts to apply this procedure to 2'-hydroxy-4'-methoxyacetophenone (peonol) have not been successful, oily products resulting. Highly reactive aldehydes such as 2,4-dichlorobenzaldehyde, *p*-nitrobenzaldehyde and *p*-trifluoromethylbenzaldehyde also yield unsatisfactory products under the conditions detailed in this paper. Both of these problems are being studied in these laboratories and will be the subject of subsequent publications.

We mentioned above that Ozawa and coworkers had prepared flavonols by a one-step process similar to ours. Ozawa (2) condensed the aldehyde with the *o*-hydroxyacetophenone in alkaline methanol at 40°, removed the base, and completed the reaction in methanol at 40-50°. The reaction mixture was cooled to 0°, and 15 percent hydrogen peroxide added slowly. The mixture was allowed to stand and the flavonol isolated by adding dilute sulfuric acid. Using this procedure on 15-30 grams of the *o*-hydroxyacetophenone, they prepared the following flavonols (name, % yield, m.p. given): 3',4'-dimethoxyflavonol, 71%, m.p. 198-200°; 3',4'-methylenedioxyflavonol, 51%, m.p. 212-213°; 6-chloro-3',4'-dimethoxyflavonol, 65%, m.p. 244-245°; 6-methyl-3',4'-methylenedioxyflavonol, 35%, m.p. 195-196°.

TABLE I

Data on Direct Flavonol Preparation from *o*-Hydroxyacetophenone (10 g., 0.74 mole) and Certain Benzaldehydes



Ar.	Wt. ArCHO	Crude Product Wt, % yield, m.p.
Phenyl	7.8 g.	9.4 g., 54%, 168-170° (a)
<i>p</i> -Methoxyphenyl	10.0 g.	11.7 g., 59%, 231-232° (b)
3,4-Dimethoxyphenyl	12.2 g.	11.1 g., 51%, 192-200° (c)
<i>p</i> -Tolyl	8.8 g.	12.3 g., 67%, 196-198° (d)
3,4-Methylenedioxyphenyl	11.0 g.	12.7 g., 61%, 214-215° (e)
<i>p</i> -Chlorophenyl	10.3 g.	10.7 g., 52%, 171-185° (f)

(a) m.p. 169°, reference (10); (b) m.p. 233-234°, reference (5); (c) m.p. 201-202°, reference (5); (d) *Anal.* Calcd. for C₁₆H₁₂O₃: C, 76.18; H, 4.79. Found: C, 76.26; H, 5.02; (e) m.p. 214-215°, reference (11); (f) Recrystallized from ethanol, 85 ml./g., m.p. 203-205°, 61% recovery; m.p. 198°, reference (12).

EXPERIMENTAL

The results in Table I are those obtained in the following standard procedures. Three solutions were prepared. In solution A, 73.5 mmoles (10.0 g.) of *o*-hydroxyacetophenone and an equivalent amount of the benzaldehyde were dissolved in 100 ml. of alcohol. Solution B consisted of 10 g. of sodium hydroxide in 15 ml. of water. Solution C was prepared by mixing 25 ml. of a sodium hydroxide solution (1 g./5 ml.) with 500 ml. of 95% ethanol. The observations detailed below were made during the preparation of flavonol itself. Similar phenomena, differing only slightly in detail, took place in all of the preparations.

The condensation of the benzaldehyde and *o*-hydroxyacetophenone was carried out by mixing solutions A and B with vigorous stirring. A heavy precipitate formed at once, presumably the salt of the *o*-hydroxyacetophenone. This mixture gradually became warm and more fluid. Vigorous stirring was required here as the salt of the chalcone soon began to precipitate and the mixture eventually set to a firm paste. This paste was allowed to stand overnight and then dissolved in solution C. A Waring blender was effective here. It was not necessary to wait until all of the solid had dissolved. After cooling to 15°, the peroxide was added quickly with stirring. As the oxidation mixture stood, the temperature rose. Between 30 and 50°, the mixture changed from a deep reddish orange to green, and bubbles of gas were evolved as the mixture reverted to a reddish color. With larger batches the temperature sometimes rose above 50°. The mixture was cooled to room temperature and neutralized with dilute sulfuric acid. A mixture of flavonol and the inorganic sulfate precipitated. The latter dissolved when the acidified solution was poured into a large volume of water. After standing for some time, the flavonol was collected by filtration.

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