A NEW GENERAL METHOD FOR THE SYNTHESIS OF THE DERIVATIVES OF FLAVONOL.*

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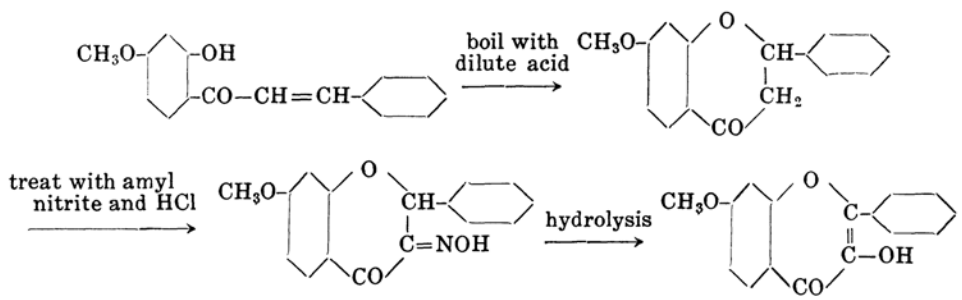
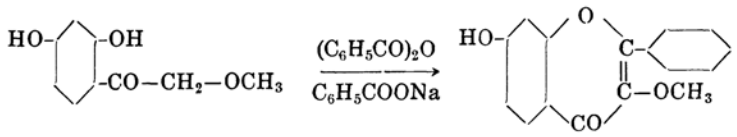
The derivatives of flavonol were first synthesised by Kostanecki and Lampe[1] from the derivatives of *o*-hydroxychalkone through isonitroso-flavanones, as shown in the following scheme:



* Translation from the original, *J. Chem. Soc. Japan*, **55** (1934), 1256.

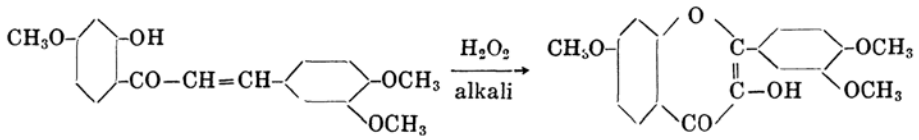
(1) *Ber.*, **37** (1904), 773.

About ten years ago, Robinson and Allan[2] suggested a new general method for their preparation:



By means of these methods a large number of the derivatives of flavonol have hitherto been synthesised.

The present author has observed that the derivatives of *o*-hydroxychalkone show an extreme facility in forming derivatives of flavonol by the action of hydrogen peroxide in the presence of alkali. A methyl alcoholic solution of 4,3′,4′-trimethoxy-2-hydroxychalkone containing hydrogen peroxide and alkali was kept at 0–5° for 12 hours, and, on acidifying, a pale yellow substance separated out. This substance, melting at 185°, was proved to be identical with 7,3′,4′-trimethoxy-3-hydroxyflavone by the mixed melting point. The yield amounted to about 80%.

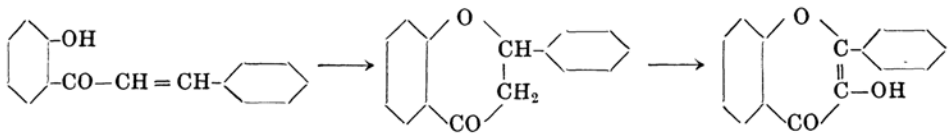


The similar reactions were carried out with 2-hydroxychalkone, 2-hydroxy-4′-methoxychalkone, and 2-hydroxy-3′,4′-dimethoxychalkone, and the corresponding derivatives of flavonol were obtained in good yields. It can naturally be considered that this method is generally applicable for synthesis of the derivatives of flavonol. Owing to the simplicity of the procedure and to the excellent yield, it may be said to be a new convenient method for preparation.

Weitz and Scheffer[3] first studied the action of hydrogen peroxide on chalkone in the aqueous-alcoholic solution and obtained benzalacetophenone-oxide from benzalacetophenone. Recently, Baker and Robinson[4] applied this reaction to 2-acetoxy-4-methoxychalkone, but without success, and reported that the reaction resulted merely in the hydrolysis of the acetoxy-group. But the present author has observed that the above-mentioned derivatives of *o*-hydroxychalkone easily give the correspond-

(2) *J. Chem. Soc.*, **125** (1924), 2192.
(3) *Ber.*, **54** (1921), 2344.
(4) *J. Chem. Soc.*, **1932**, 1798.

ing flavonols under the conditions described above. Now it is interesting to consider the mechanism of the formation of flavonol from *o*-hydroxychalkone. We first suppose that the formation of the oxide as an intermediate product may take place, but it is difficult to explain how the oxide is converted into flavonol. On the other hand, we can also consider that *o*-hydroxychalkone isomerises to flavanone which may be oxidised to flavonol under these conditions. The latter view was supported by the experimental fact that *o*-hydroxychalkone easily gives flavanone with alkali alone and the resulting flavanone is subsequently converted into flavonol in an excellent yield by the action of hydrogen peroxide in the presence of alkali. Hence, the mechanism of the formation of flavonol is accounted for by the following scheme:



That of the formation of the other three derivatives of flavonol will also be explained as in the above case.

By the action of hydrogen peroxide in the presence of alkali, 4′-methoxyflavanone and 7,3′,4′-trimethoxyflavanone were oxidised to 4′-methoxyflavonol and 7,3′,4′-trimethoxyflavonol respectively in good yields. It is of interest to note that a derivative of flavanone is directly converted into a derivative of flavonol by such a simple oxidation. In the early stage of the investigation of the derivatives of flavonol, attempts to obtain flavonol from flavone by oxidation were made by Kostanecki and his collaborators,[5] but without success. The present author has succeeded in preparing it from flavanone by oxidation.

Experimental.

Preparation of 7, 3′, 4′-Trimethoxy-3-hydroxyflavone from 4, 3′, 4′-Trimethoxy-2-hydroxychalkone. To a solution of 4,3′,4′-trimethoxy-2-hydroxychalkone (1.5 g.) in methyl alcohol (30 c.c.), 15% aqueous hydrogen peroxide (4 c.c.) and 16% aqueous sodium hydroxide (10 c.c.) were added under cooling. After being allowed to stand at 0–5° for 12 hours, the solution was acidified with dilute sulphuric acid and diluted with water. The precipitate was recrystallised from alcohol, pale yellow needles melting at 185°, and showing no depression of melting point by admixture with 7,3′,4′-trimethoxy-3-hydroxyflavone synthesized by the Kostanecki method. The yield was 1.2 g. (Found: C, 65.62; H, 5.05. Calc. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.87%.)

(5) *Ber.*, **35** (1902), 1679.

Preparation of 3-Hydroxyflavone (Flavonol) from o-Hydroxychalkone. *o*-Hydroxychalkone (1 g.) was dissolved in methyl alcohol (20 c.c.), and 15% aqueous hydrogen peroxide (3 c.c.) and 16% aqueous sodium hydroxide (5 c.c.) were added. After standing overnight in the ice-chest, the solution was acidified with dilute sulphuric acid and diluted with water, when a colourless substance separated out. It was recrystallised from alcohol, needles melting at 169–170°. This melting point coincides with that of flavonol.[6] The yield was 0.8 g. (Found: C, 75.35; H, 4.58. Calc. for $C_{15}H_{10}O_3$: C, 75.63; H, 4.20%.)

3-Methoxyflavone (Methylflavonol). 3-Hydroxyflavone (0.5 g.) was methylated with diazomethane in ethereal solution. On recrystallising from alcohol, colourless needles, m.p. 114°, were obtained. The yield was 0.5 g. 3-Methoxyflavone which prepared by Hattori[7] melts at 107°. (Found: C, 75.97; H, 4.98. Calc. for $C_{16}H_{12}O_3$: C, 76.19; H, 4.76%.)

3-Acetoxyflavone. 3-Hydroxyflavone (0.5 g.) was acetylated with acetic anhydride and fused sodium acetate. The product forms colourless crystals melting at 110–111°. Kostanecki and Szabranski[8] gave 110-111° as its melting point. Yield, 0.2 g. (Found: C, 73.00; H, 4.56. Calc. for $C_{17}H_{12}O_4$: C, 73.21; H, 4.29%.)

Preparation of 4′-Methoxy-3-hydroxyflavone from 4′-Methoxy-2-hydroxychalkone. To a solution of 4′-methoxy-2-hydroxychalkone (1 g.) in methyl alcohol (35 c.c.), 15% aqueous hydrogen peroxide (2 c.c.) and 16% aqueous sodium hydroxide (2 c.c.) were added under cooling. After standing overnight in the ice-chest, the solution was acidified with dilute sulphuric acid and diluted with water. The pale yellow crystals which separated were collected and recrystallised from alcohol, pale yellow needles, m.p. 230–232°. Edelstein and Kostanecki[9] gave 231–232° as the melting point. Yield, 0.7 g. (Found: C, 71.57; H, 4.70. Calc. for $C_{16}H_{14}O_4$: C, 71.64; H, 4.48%.)

3,4-Dimethoxyflavone. 4′-Methoxy-3-hydroxyflavone (0.5 g.) was methylated with diazomethane in ethereal solution. The raw product was recrystallised from alcohol, when it melted at 90–92°. The yield was 0.3 g. (Found: C, 72.15; H, 5.21. Calc. for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96%.)

Preparation of 3′,4-Dimethoxy-3-hydroxyflavone from 3′,4′-Dimethoxy-2-hydroxychalkone. 3′,4′-Dimethoxy-2-hydroxychalkone (1.3 g.) was dissolved in methyl alcohol (15 c.c.), and 15% aqueous hydrogen peroxide (2 c.c.) and 16% aqueous sodium hydroxide (3 c.c.) were added under cooling. After standing overnight in the ice-chest, the alkaline solution was acidified with dilute sulphuric acid and diluted with water, when a yellow substance separated out. On recrystallising from alcohol, pale yellow crystals m.p. 200–202° were obtained. Hattori[10] gave 202° as its melting point. Yield, 1 g. (Found: C, 68.66; H, 4.84. Calc. for $C_{17}H_{14}O_5$: C, 68.79; H, 4.69%.)

3,3′,4′-Trimethoxyflavone. 3′,4′-Dimethoxy-3-hydroxyflavone (0.5 g.) was methylated with diazomethane in ethereal solution and the product was then purified, when

(6) *Ber.*, **37** (1904), 2820.
(7) *Acta Phytochimica*, **4** (1928), 44.
(8) *Ber.*, **37** (1904), 2820.
(9) *Ber.*, **38** (1905), 1507.
(10) This Bulletin, **2** (1927), 175.

almost colourless crystals, m.p. 168–169°, were obtained. Hattori[10] gave 168–169° as its melting point. The yield was 0.2 g. (Found: C, 69.04; H, 5.36. Calc. for $C_{18}H_{16}O_5$: C, 69.23; H, 5.12%.)

Preparation of Flavanone from *o*-Hydroxychalkone. To a solution of *o*-hydroxychalkone (1 g.) in methyl alcohol (15 c.c.), 16% aqueous sodium hydroxide (4 c.c.) was added. After standing overnight in the ice-chest, the solution was diluted with water, when a colourless substance separated out. On recrystallising from dilute alcohol, colourless prisms, m.p. 75–76°, were obtained. No alternation of melting point was observed on mixing it with flavanone obtained by the usual method. Yield, 0.8 g.

Preparation of 3-Hydroxyflavone (Flavonol) from Flavanone. Flavanone (0.3 g.) in methyl alcohol (15 c.c.) was mixed with 15% aqueous hydrogen peroxide (2 c.c.) and 16% sodium hydroxide (3 c.c.) under cooling. After standing overnight in the ice-chest, the solution was acidified with dilute sulphuric acid and diluted with water. The colourless crystals which separated were recrystallised from alcohol, colourless needles, m.p. 169–170°. No alternation of melting point was observed on mixing it with flavonol obtained by the method described on page 185. Yield, 0.25 g.

Preparation of 4′-Methoxy-3-hydroxyflavone from 4′-Methoxyflavanone. 4′-Methoxyflavanone (0.5 g.) was dissolved in methyl alcohol (10 c.c.), and 15% aqueous hydrogen peroxide (2 c.c.) and 16% aqueous sodium hydroxide (2 c.c.) were added under cooling. After standing overnight in the ice-chest, the solution was acidified with dilute sulphuric acid and diluted with water, when a pale yellow substance separated out. It was recrystallised from alcohol, pale yellow needles, m.p. 232°. It proved to be identical with 4′-methoxy-3-hydroxyflavone by the mixed melting point. Yield, 0.4 g.

Preparation of 7, 3′, 4′-Trimethoxy-3-hydroxyflavone from 7, 3′, 4′-Trimethoxyflavanone. 7,3′,4′-Trimethoxy-3-hydroxyflavone was directly prepared from 7,3′,4′-trimethoxyflavanone similarly as described above.

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