Avery Laboratory, The University of Nebraska

A High-Yield Modification of the Baker-Venkataraman Rearrangement. Application to the Synthesis of 5-Hydroxyflavone and 6,8-Dichloro-5-hydroxyflavone

J. H. Looker, James R. Edman (1), and J. I. Dappen

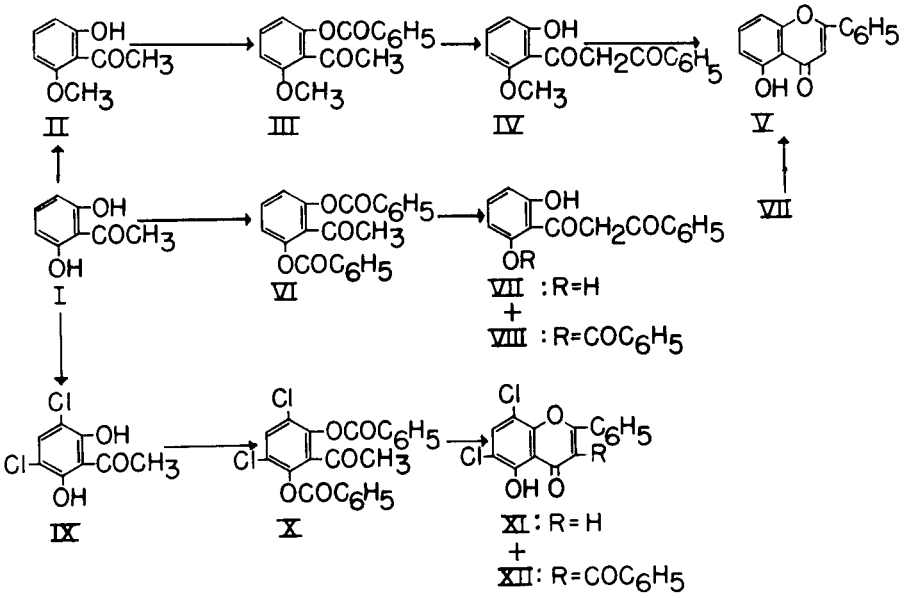
A three-step synthesis of 5-hydroxyflavone in 80% yield from 2,6-dihydroxyacetophenone is described. The key step is a modification of the Baker-Venkataraman rearrangement in which small amounts of water are deliberately introduced. Characterization of the primary rearrangement products, 1-(2,6-dinydroxyphenyl)-3-phenyl-1,3-propanedione, and 1-(2-benzoyloxy-6-hydroxyphenyl)-3-phenyl-1,3-propanedione, is reported. Application of the synthesis to 3,5-dichloro-2,6-dihydroxyacetophenone gives a mixture of 6,8-dichloro-5-hydroxyflavone and its 3-benzoyl derivative. Infrared spectral data are presented for several intermediates and flavones, and indicate the utility of the previously described infrared spectral method for detecting 3-aroylflavones.

The synthesis of 5-hydroxyflavone, a pigment isolated (2) from a deposit on *Primula imperialis* var. *gracilis*, has been investigated by several workers since the first synthesis by Sugasawa (3). The essential starting material, 2,6-dihydroxyacetophenone, is obtained (4) in a multi-step synthesis from β-methylumbelliferone. In the first synthesis, 5-hydroxyflavone was obtained by use of the Allan-Robinson method (5), although the yield in this procedure was unsatisfactory (6). However, application of the Baker-Venkataraman rearrangement (7) to 2,6-dibenzoyloxyacetophenone has led to 3-benzoyl-5-hydroxyflavone (6, 8) as the principal product, which gives 5-hydroxyflavone only after treatment with aluminum chloride (6). Seshadri and associates have reported (9) the preparation of 5-hydroxyflavone from 3-benzoyl-5-hydroxyflavone by cleavage of the 3-aroyl group with alcoholic sodium carbonate, but the utility of this method remains controversial (8, 10). It is apparent that a completely satisfactory synthesis of 5-hydroxyflavone has not been previously available. Recent interest in this substance results from the anomalous infrared carbonyl absorption, the frequency of which does not shift to lower values under the influence of the hydrogen bond (11, 12).

Inasmuch as 3-benzoyl-5-hydroxyflavone, instead of 5-hydroxyflavone, has been obtained as the main product in both the Allan-Robinson method with 2,6-dihydroxyacetophenone (I) (3, 9) and the Baker-Venkataraman rearrangement of 2,6-dibenzoyloxyacetophenone (6, 8), the synthetic route (9) from 2-methoxy-6-benzoyloxyacetophenone was reinvestigated. Rearrangement of two benzoyl groups in 2-methoxy-6-benzoyloxyacetophenone to give a triaroylmethane derivative, which would undergo ring-closure to the 3-benzoyl derivative, is obviously impossible. The general procedure of Seshadri (9) has been followed, with several refinements, the most significant of which is use of hydriodic acid to effect demethylation and ring-closure of IV in a single step. In our hands, the four steps of methylation to 2-hydroxy-6-methoxyacetophenone (II), benzoylation to form III, rearrangement to the diketone IV, and single-step ring-closure and demethylation gave an overall 22% yield of 5-hydroxyflavone (V). The method has the advantage of yielding very pure V, m.p. 157.5-158.5°.

A shorter synthesis proceeds from 2,6-dibenzoyloxyacetophenone (VI), readily available in high yield by benzoylation of I. By using alkali metal hydroxides containing small amounts of water, and effecting rearrangement of VI at room temperature, we have obtained 5-hydroxyflavone as the predominant cyclization product of the initially formed diaroylmethane derivatives. Apparently formation of triaroylmethanes does not occur to an appreciable extent. Thus, 2,6-dibenzoyloxyacetophenone (VI) undergoes rearrangement in pyridine at room temperature with potassium hydroxide containing approximately 10% water to give 1-(2,6-dihydroxyphenyl)-3-phenyl-1,3-propanedione (VII), which is accompanied by a small amount of 1-(2-benzoyloxy-6-hydroxyphenyl)-3-phenyl-1,3-propanedione (VIII). These two rearrangement products were isolated and characterized. However, the crude 1-(2,6-dihydroxyphenyl)-3-phenyl-1,3-propanedione was of purity sufficient for cyclization with acetic acid to 5-hydroxyflavone (V) in 51% yield (based on I). The diketone VIII was cyclized to 5-benzoyloxyflavone, identical with the product from benzoylation of V.

Although the yield of V in the immediately preceding procedure was satisfactory, the synthesis of choice employed powdered sodium hydroxide and VI



in pyridine at room temperature for the Baker-Venkataraman rearrangement, and consistently resulted in yields of V in excess of 80% (based on I). The method for preparing powdered sodium hydroxide undoubtedly led to the introduction of undetermined, small quantities of water. It is probable that sodium hydroxide catalyzes hydrolytic cleavage of one benzoyloxy group of either 2,6-dibenzoyloxyacetophenone (VI) or 1-(2-benzoyloxy-6-hydroxyphenyl)-3-phenyl-1,3-propanedione (VIII), thus precluding formation of a triaroylmethane through oxygen-to-carbon rearrangement of both benzoyl groups. The superior yield of 5-hydroxyflavone from rearrangement of 2,6-dibenzoyloxyacetophenone in pyridine with sodium hydroxide, as opposed to potassium hydroxide, could be due either to the greater effectiveness of sodium hydroxide in the heterogeneous mixture in catalyzing hydrolysis of one benzoyloxy group, or to the smaller amount of water present when sodium hydroxide was used. Even moderate amounts of water might hydrolyze both benzoyloxy groups of 2,6-dibenzoyloxyacetophenone and prevent rearrangement of the one aroyloxy group essential for synthesis of 5-hydroxyflavone.

3,5-Dichloro-2,6-dihydroxyacetophenone (IX), the intermediate required for preparation of 6,8-dichloro-5-hydroxyflavone, was obtained by chlorination of 2,6-dihydroxyacetophenone (I). In the assignment of structure to the chlorination product, it is assumed that the usual directive influences make halogenation at the 4-position of I unlikely. The dibenzoate (X) was subjected to the rearrangement conditions previously outlined, but in this case a mixture of 6,8-dichloro-5-hydroxyflavone (XI) and its 3-benzoyl derivative (XII) was obtained. The intermediate diketone was not obtained in a pure state, but apparently was contaminated with the triaroylmethane. After cyclization, XII was obtained and readily purified. The infrared spectrum of XII contained a strong band at 1677 cm^{-1}, attributable to the 3-aroyl keto stretching vibration (8). Pure 6,8-dichloro-5-hydroxyflavone was obtained only after elaborate purification.

EXPERIMENTAL

Melting points are uncorrected. Analyses are by Micro-Tech Laboratories, Skokie, Illinois. Unless otherwise indicated, infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrophotometer.

2,6-Dibenzoyloxyacetophenone.

To 100 g. of 2,6-dihydroxyacetophenone in 300 ml. of warm pyridine was added 200 ml. benzoyl chloride. The mixture was heated 90 min. on a steam bath, and then poured onto 1.5 l. of ice-water to which 300 ml. conc. hydrochloric acid was added. The precipitated product was collected and recrystallized from methanol (charcoal); yield, 213 g. (90%), m.p. 102-103° (lit. (4) m.p. 106°).

5-Hydroxyflavone. A. Baker-Venkataraman Rearrangement of 2,6-Dibenzoyloxyacetophenone Utilizing Potassium Hydroxide.

2,6-Dibenzoyloxyacetophenone, m.p. 104-105° (10 g.) was dissolved in 60 ml. of pyridine and the resulting pyridine solution added to 15 g. of powdered reagent grade potassium hydroxide pellets (containing approximately 10% water). The reaction mixture was shaken at room temperature for 4 hr. The resulting greenish-brown suspension was poured onto a mixture of 100 ml. concentrated hydrochloric acid and 500 ml. of ice. The gum which formed initially was recrystallized from methanol to give a yellow crystalline product (Y), which was collected by filtration. The methanol mother liquor was evaporated to dryness on a flash evaporator, and the residue heated with 100 ml. of glacial acetic acid for 2 hr. Dilution of the acetic acid solution with water gave 5-hydroxyflavone, which was recrystallized from absolute ethanol; yield, 3.36 g. (51%), m.p. 152-155° (lit. (4) m.p. 156-157°).

B. Baker-Venkataraman Rearrangement of 2,6-Dibenzoyloxyacetophenone Utilizing Sodium Hydroxide.

A 45 g. quantity of reagent grade sodium hydroxide pellets (97%) was weighed out as rapidly as possible, transferred to a large mortar, covered with anhydrous ether, and ground until no large pieces remained. The ether was removed by distillation *in vacuo*. To the residual powdered sodium hydroxide was added a solution of 40 g. of 2,6-dibenzoyloxyacetophenone in 375 ml. of pyridine. The reaction mixture was shaken at room temperature in a tightly stoppered flask for 4 hr. The greenish-brown suspension then was poured onto a large quantity of crushed ice to which 400 ml. of conc. hydrochloric acid previously had been added. An oily product, which sometimes crystallized slowly, resulted. The aqueous phase was removed by decantation, and the residual oil dissolved in hot methanol (charcoal). Evaporation of the methanol from the filtrate gave either a butter-yellow solid or viscous sirup (Product Z). For cyclization to the flavone, 300 ml. of glacial acetic acid was added to the solid or sirup and the mixture heated under reflux for 2 hr. The acetic acid solution was poured onto about 1.6 l. of ice, and the precipitated 5-hydroxy-

flavone collected by filtration and washed thoroughly with cold water; yield of dried product, 24 g. (81% based on 2, 6-dihydroxyacetophenone), m.p. 155-156° (lit. (3) m.p. 156-157°). The solid state infrared spectrum was identical with that previously reported (12) for 5-hydroxyflavone.

C. From 2-Hydroxy-6-methoxyacetophenone.

2, 6-Dihydroxyacetophenone was methylated by the method of Baker to give 2-hydroxy-6-methoxyacetophenone, m.p. 57-59° (lit. (13) m.p. 60°), in 73% yield.

2-Hydroxy-6-methoxyacetophenone (10 g.) was dissolved in 40 ml. of pyridine and 12 ml. of benzoyl chloride added. The pyridine solution was heated under reflux for 3 hr., cooled, and poured into 150 ml. of dilute hydrochloric acid. The resulting orange oil solidified upon cooling the acid mixture, and was collected by filtration. After recrystallization from methanol, the yield of white solid, m.p. 62-63°, was 8.6 g. (53%). This substance previously was described (9) as a pale yellow viscous oil.

To a stirred solution of 10 g. of the benzoylation product, m.p. 62-63°, in 40 ml. of dry pyridine was added 15 g. of potassium hydroxide (previously powdered inside a dry box at room temperature by grinding in a mortar). After being stirred 4 hr. at room temperature, the reaction mixture yielded a brownish-yellow solid. The total mixture was poured into 100 ml. of dilute hydrochloric acid to give an orange oil which solidified after 30 min. Recrystallization gave 6.7 g. (67%) of the bright yellow 1-(2-hydroxy-6-methoxyphenyl)-3-phenyl-1, 3-propanedione which melted at 86-106° (lit. (14) m.p. 96-98°). The melting point range for our product probably results from contamination with 5-methoxyflavone.

A solution of 5 g. of 1-(2-hydroxy-6-methoxyphenyl)-3-phenyl-1, 3-propanedione in 40 ml. of glacial acetic acid and 25 ml. of hydriodic acid (sp. gr. 1.5) was heated under reflux for 2 hr. The solution then was poured into 100 ml. of nearly saturated sodium bisulfite solution. A flocculent yellow precipitate formed, which was collected by filtration, washed with water, and recrystallized from ethyl acetate-ethanol-water; yield, 3.7 g. (84%) of light yellow 5-hydroxyflavone, m.p. 157.5-158.5°.

1-(2-Hydroxy-6-methoxyphenyl)-3-phenyl-1, 3-propanedione (6.1 g.) was converted to 5-methoxyflavone upon standing in 40 ml. of concentrated sulfuric acid for 4 hr. Dilution by addition of the acid solution to 100 g. of ice, followed by recrystallization of the resulting solid from ethanol-water gave 5.2 g. (91%) of colorless 5-methoxyflavone, m.p. 126-129° (lit. (9) m.p. 130-131°).

1-(2-Benzoyloxy-6-hydroxyphenyl)-3-phenyl-1, 3-propanedione.

Product Y from Procedure A above (0.9 g., 9%) was recrystallized once from methanol, then three times from acetone to give the yellow, crystalline substance, m.p. 175°. After drying over phosphorus pentoxide *in vacuo* for two days, the pure, dry compound, m.p. 177.5-178.5° was obtained.

Anal. Calcd. for $C_{22}H_{16}O_5$: C, 73.32; H, 4.48. Found: C, 73.44; H, 4.72.

The infrared spectrum (potassium bromide disk) contained bands at 3150 (O-H stretching), 1737 (ester CO), 1693 (keto CO), and 1626 cm^{-1} (H-bonded keto CO).

1-(2, 6-Dihydroxyphenyl)-3-phenyl-1, 3-propanedione.

Product Z from Procedure B above was recrystallized three times from cyclohexane. The light yellow substance, m.p. 154-155.5° was soluble in dilute sodium hydroxide and gave a positive ferric chloride test.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.74; H, 4.82.

The infrared spectrum (potassium bromide disk) contained bands at 3480 (O-H stretching), 1663 (keto CO), 1632 cm^{-1} (H-bonded keto CO).

5-Benzoyloxyflavone. A. From 5-Hydroxyflavone.

To a solution of 1 g. of 5-hydroxyflavone in 20 ml. of dry pyridine was added 0.65 ml. of benzoyl chloride. The reaction mixture was heated 3 hr. on a steam bath, and then stood overnight at room temperature. The precipitate present was collected by filtration and washed with dilute hydrochloric acid. Two crystallizations from absolute ethanol and one from acetone gave analytically pure 5-benzoyloxyflavone, m.p. 181-181.5°.

Anal. Calcd. for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 76.96; H, 4.39.

The infrared spectrum (potassium bromide disk) contained ester and flavone carbonyl bands at 1735 and 1650 cm^{-1}, respectively.

B. From Cyclization of 1-(2-Benzoyloxy-6-hydroxyphenyl)-3-phenyl-1, 3-propanedione.

1-(2-Benzoyloxy-6-hydroxyphenyl)-3-phenyl-1,3-propanedione (3.7 g., m.p. 165-170°) was dissolved in 50 ml. glacial acetic acid and the solution heated under reflux for 2 hr. The reaction mixture was poured into 150 ml. of water, and the precipitated colorless product collected by filtration and washed thoroughly with water. Recrystallization from absolute ethanol (charcoal) gave 1.4 g. of 5-benzoyloxyflavone, m.p. and mixture m.p., 180-181°.

3, 5-Dichloro-2, 6-dihydroxyacetophenone.

Gaseous chlorine was bubbled for 5 min. at 0° through a stirred solution of 10 g. of 2, 6-dihydroxyacetophenone in 75 ml. of ethanol. After standing an additional 5 min., the mixture was diluted with water and filtered to give 12.2 g. (84%) of crude yellow product. Two crystallizations from absolute ethanol gave analytically pure 3, 5-dichloro-2, 6-dihydroxyacetophenone, m.p. 174.5-175°.

Anal. Calcd. for $C_8H_6Cl_2O_3$: C, 43.46; H, 2.71; Cl, 32.10. Found: C, 43.63; H, 2.80; Cl, 32.19.

The substance in aqueous acetone gave a negative test with aqueous silver nitrate. The infrared spectrum (chloroform solution, 1 mm. cell in Perkin-Elmer Model 237 Grating Spectrophotometer) contained bands at 3510 (O-H stretching) and 1635 cm^{-1} (H-bonded CO).

3, 5-Dichloro-2, 6-dibenzoyloxyacetophenone.

To a solution of 5 g. of 3, 5-dichloro-2, 6-dihydroxyacetophenone in 15 ml. of pyridine was added a 6.45 g. quantity of benzoyl chloride. The resulting reaction mixture was heated on a steam bath for 30 min., and then poured onto ice and excess concentrated hydrochloric acid. The separated product was recrystallized from methanol (charcoal) to give 8.2 g. (84.5%) of the colorless dibenzoate, m.p. 134-135°. Further crystallization from methanol gave the analytically pure substance, m.p. 135-136° (change in crystalline form at 121°).

Anal. Calcd. for $C_{22}H_{14}Cl_2O_5$: C, 61.55; H, 3.26; Cl, 16.53. Found: C, 62.01; H, 3.65; Cl, 16.33.

The infrared spectrum (chloroform solution, 0.1 mm. cell in Perkin-Elmer Model 237 Grating Spectrophotometer) contained ester carbonyl bands at 1757 and 1741, and a keto carbonyl band at 1704 cm^{-1}.

Baker-Venkataraman Rearrangement of 3, 5-Dichloro-2, 6-dibenzoyloxyacetophenone.

A solution of 25 g. of 3, 5-dichloro-2, 6-dibenzoyloxyacetophenone in 236 ml. pyridine was added to 22.8 g. of powdered sodium hydroxide, prepared as in Procedure B for 5-hydroxyflavone. The resulting mixture was shaken in a tightly stoppered flask at room temperature for 4 hr., and then was poured onto excess ice-concentrated hydrochloric acid. After standing overnight, a viscous oil was present in the aqueous mixture. The aqueous phase was removed by decantation. The oily residue was heated in boiling methanol, and the insoluble material present collected by filtration; yield, 10.8 g., m.p. 205-230°. The methanol filtrate (M) was retained. An 8.0 g. quantity of product was heated under reflux for 2 hr. in 180 ml. glacial acetic acid. The mixture was diluted with water, and the resulting insoluble material collected by filtration; yield, 6.5 g., m.p. 195-218°. This latter product was heated under reflux in boiling absolute ethanol on a steam bath for 3 hr. Two different crystal modifications were present in the ethanol: fine, hair-like yellow needles which were readily removed along with the ethanol by decantation, and dark yellow rods which remained as residue after decantation. The latter residue was again treated with boiling absolute ethanol, and an additional fraction of fine yellow needles removed by decantation. The 6, 8-dichloro-5-hydroxy-3-benzoylflavone which remained as residue was recrystallized twice from chloroform to give the analytically pure substance: m.p. 240-241°.

Anal. Calcd. for $C_{22}H_{12}Cl_2O_4$: C, 64.24; H, 2.92; Cl, 17.26. Found: C, 64.22; H, 3.21; Cl, 17.85.

The infrared spectrum (chloroform solution, 1 mm. cell) contained the 3-benzoyl carbonyl band at 1677 and the flavone carbonyl band at 1643 cm^{-1}.

The methanol filtrate (M) yielded 1.6 g. of crystalline material which was collected by filtration and discarded (filtrate N retained). Solvent removal *in vacuo* from filtrate N left a residual gum, which was heated under reflux for 2 hr. in 150 ml. of glacial acetic acid. The product precipitated by dilution with water was collected by filtration; yield, 3.6 g., m.p. 234-237°. After one recrystallization from absolute ethanol, the product melted 232-235°. The substance then was partially dissolved in hot absolute ethanol, the mixture filtered, and the precipitate discarded. The ethanol filtrate gave long, fine, hair-like needles of 6, 8-dichloro-5-hydroxyflavone, which after one additional crystallization from absolute ethanol, was analytically pure; m.p. 234°.

Anal. Calcd. for $C_{15}H_8Cl_2O_3$: C, 58.65; H, 2.62; Cl, 23.08. Found: C, 58.74; H, 2.80; Cl, 22.92.

The infrared spectrum (potassium bromide disk) contained the flavone carbonyl band at 1654 cm^{-1}.

6, 8-Dichloro-5-benzoyloxyflavone.

6,8-Dichloro-5-hydroxyflavone (1 g.), in 20 ml. of pyridine, was benzoylated with 0.51 ml. of benzoyl chloride. Reaction conditions and isolation were as described for 5-benzoyloxyflavone. The crude product was recrystallized from chloroform-absolute ethanol and then from absolute ethanol alone to give the analytically pure substance, m.p. 248- 249°.

Anal. Calcd. for $C_{22}H_{12}Cl_2O_4$: C, 64.24; H, 2.92; Cl, 17.26. Found: C, 64.07; H, 3.04; Cl, 17.39.

The infrared spectrum (potassium bromide disk) contained ester and flavone carbonyl bands at 1745 and 1653 cm^{-1}, respectively.

6,8-Dichloro-5-benzoyloxy-3-benzoylflavone.

6,8-Dichloro-5-hydroxy-3-benzoylflavone (0.5 g.) in 10 ml. of pyridine, was benzoylated with 0.20 ml. of benzoyl chloride, using the reaction and isolation procedures described for 5-benzoyloxyflavone. The crude benzoate was recrystallized twice from chloroform-absolute ethanol to give the analytically pure substance, m.p. 233-234°.

Anal. Calcd. for $C_{29}H_{16}Cl_2O_5$: C, 67.58; H, 3.11. Found: C, 67.49; H, 3.37.

The infrared spectrum (chloroform solution, 1 mm. cell) contained bands at 1751 (ester CO), 1683 (3-benzoyl CO), and 1648 cm^{-1} (flavone CO).

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