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Synthesis of 5-Hydroxy-4′-iodoflavone and Some Related Compounds

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5-Methoxy-4′-nitroflavone, 4′-iodo-5-methoxyflavone, and 5-hydroxy-4′-methoxyflavone have been prepared by cyclisation of the corresponding 1,3-diaroylpropane-1,3-dione. 4′-Iodo-5-methoxyflavone was subsequently demethylated to 5-hydroxy-4′-iodoflavone. The Baker-Venkataraman rearrangement of 2,6-bis(*p*-nitrobenzoyloxy)-acetophenone yielded 5-hydroxy-3-(*p*-nitrobenzoyl)-4′-nitroflavone.

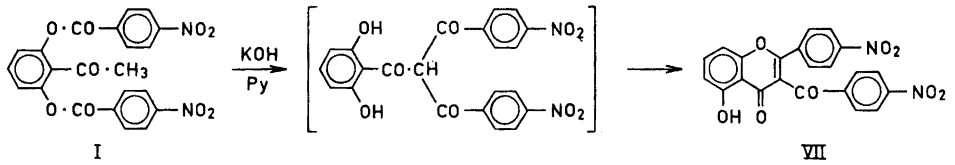
Certain organic compounds containing a carbonyl group and a phenolic or enolic hydroxy group in the *peri* positions of two condensed rings, such as alizarin,[1] sodium alizarin-3-sulphonate,[2,3] and tetracyclines,[4,5] have been shown to have affinity for bone tissues and are able to colour them. This property seems to depend on their ability to form chelate bonds with calcium ions on the surface of the bone tissue. Compounds with such properties might be useful in the diagnosis of metastatic neoplasms in bone tissue.[3] In connection with investigations in this field, we turned our attention to 5-hydroxyflavones in which iodine was introduced to facilitate the localisation of the compounds by means of X-rays or by tracer methods using radioactive iodine. This paper describes the synthesis of 5-hydroxy-4′-iodoflavone and some related compounds.

Our original intention was to prepare the desired iodoflavone through suitable intermediates containing a nitro group, which could be reduced to the amino group and replaced by iodine.

Treating 2,6-dihydroxyacetophenone with one equivalent of *p*-nitrobenzoyl chloride in pyridine gave a mixture of 2,6-bis-(*p*-nitrobenzoyloxy)acetophenone (I) and 2-hydroxy-6-(*p*-nitrobenzoyloxy)acetophenone (II) in a molar ratio of about 5:3. The amount of diacylated product formed in analogous reactions seems to be dependent on the nature of the substituent in the benzoyl chloride. Thus when the acylating agent contained the less electronegative iodine atom instead of the nitro group, the ratio of 2,6-bis(*p*-iodobenzoyloxy)acetophenone (III) to 2-hydroxy-6-(*p*-iodobenzoyloxy)acetophenone (IV) was smaller, about

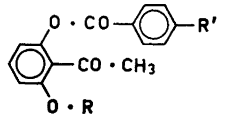
5:4, and when the aroyl chloride contained the electron-donating methoxy group in place of iodine, the amount of monoacylated product, 2-(*p*-anisoyloxy)-6-hydroxyacetophenone (V), that could be isolated from the reaction mixture under the identical experimental conditions, predominated over that of the diester VI. This last finding deviates from the results reported by Baker and Flemons,[6] who could only isolate the diester from the reaction between equivalent amounts of 2,6-dihydroxyacetophenone and *p*-anisoyl chloride. When two equivalents of *p*-anisoyl chloride were used, however, we obtained the diester VI in good yield.

When the diester I was treated with powdered potassium hydroxide in pyridine in order to effect Baker-Venkataraman transformation to the corresponding 1,3-propanedione, not only rearrangement, but also cyclisation of the rearranged product occurred, giving 5-hydroxy-3-(*p*-nitrobenzoyl)-4'-nitroflavone (VII). 3-Aroyl flavones have been obtained as the main reaction product in both the Allan-Robinson flavone synthesis [7–10] and the Baker-Venkataraman transformation of 2,6-diaroyloxyacetophenones,[11–13] a triaroylmethane derivative, formed by a double Baker-Venkataraman transformation, probably being an intermediate [9,12] (Scheme 1).



I VII

Scheme I



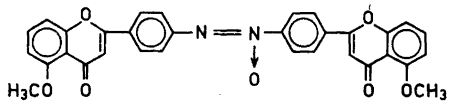
	R	R'
I	*p*-$NO_2 \cdot C_6H_4 \cdot CO$	NO_2
II	H	NO_2
III	*p*-$I \cdot C_6H_4 \cdot CO$	I
IV	H	I
V	H	OCH_3
VI	*p*-$CH_3O \cdot C_6H_4 \cdot CO$	OCH_3
VIII	CH_3	NO_2
XII	$CH_3 \cdot CO$	NO_2

The 3-aroyl group may sometimes be removed by hydrolysis.[8,10] However, attempted removal of the 3-*p*-nitrobenzoyl group from the flavone VII only resulted in unidentifiable products. The flavone VII was obtained even from the monoester II when it was treated with potassium hydroxide in pyridine. It would seem that the monoester II disproportionates to the diester I which in turn gives rise to the flavone VII. By reason of this, attempts were made

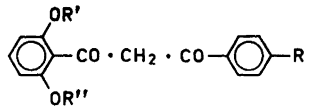
to block one of the hydroxy groups in 2,6-dihydroxyacetophenone with a protecting group that could subsequently be removed.

Reaction between 2-hydroxy-6-methoxyacetophenone and *p*-nitrobenzoyl chloride in pyridine gave 2-methoxy-6-(*p*-nitrobenzoyloxy)acetophenone (VIII) which, upon treatment with powdered potassium hydroxide in pyridine, gave 1-(2-hydroxy-6-methoxyphenyl)-3-(*p*-nitrophenyl)propane-1,3-dione (IX). This result is compatible with the finding of Rama Rao *et al.*[14] that derivatives of 2-hydroxyacetophenones containing a free hydroxyl group in the 6-position invariably give flavones directly in the Baker-Venkataraman reaction, but when the 6-position is substituted by a methoxy group, a diketone is obtained under similar conditions.

The diketone IX was cyclised to 5-methoxy-4′-nitroflavone (X) through warming it in glacial acetic acid containing concentrated sulphuric acid. Attempted demethylation with hydriodic acid or aluminium chloride did not yield the desired 5-hydroxyflavone derivative. Catalytic reduction of X with a palladium catalyst in a mixture of ethanol and ammonia was incomplete, and the product isolated analysed correctly for 4,4′-bis(5-methoxy-2-chromonyl)-azoxybenzene (XI).



XI



	R	R′	R″
IX	NO_2	H	CH_3
XIII	I	CH_3	CH_3
XVI	OCH_3	H	*p*-$CH_3O \cdot C_6H_4 \cdot CO$

In order to obviate the difficulties involved in elimination of the 5-methoxy group, it was intended to prepare 5-acetoxy-4′-nitroflavone from 2-acetoxy-6-(*p*-nitrobenzoyloxy)acetophenone (XII). The acetophenone XII was prepared in the usual manner from *p*-nitrobenzoyl chloride and 2-acetoxy-6-hydroxy-acetophenone, obtained by acylating 2,6-dihydroxyacetophenone with acetic anhydride. However, when XII was subjected to the Baker-Venkataraman reaction, a product mixture containing greater or lesser amounts of the diester I and the 3-aroylflavone VII was obtained.

Reaction between 2,6-dihydroxyacetophenone and one equivalent of *p*-iodobenzoyl chloride in pyridine gave, as has already been mentioned, a mixture of 2,6-bis(*p*-iodobenzoyloxy)acetophenone (III) and 2-hydroxy-6-(*p*-iodobenzoyloxy)acetophenone (IV). When these compounds were subjected

to the Baker-Venkataraman reaction, a complicated mixture of unidentifiable products was obtained.

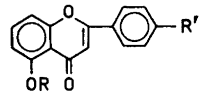
The desired 5-hydroxy-4′-iodoflavone was eventually prepared in the following way. 2,6-Dimethoxyacetophenone was condensed with ethyl *p*-iodobenzoate in the presence of sodium dust to give a compound which analysed correctly for a hydrated form of 1-(2,6-dimethoxyphenyl)-3-(*p*-iodophenyl) propane-1,3-dione (XIII).

The exact structure of this hydrated product was not ascertained. The high melting-point makes it improbable that the elements of water were present merely as water of crystallisation. Attempted demethylation of this product by heating it with pyridine hydrochloride effected only dehydration to the "normal" diketone. When the hydrated diketone XIII was moderately heated with hydriodic acid it could be cyclised to 4′-iodo-5-methoxyflavone (XIV). Prolonged heating of XIV or of the hydrated ketone XIII with hydriodic acid at 130—140° afforded 5-hydroxy-4′-iodoflavone (XV) in good yield.

The 2,6-dimethoxyacetophenone used as starting material for the above synthesis could be obtained conveniently in good yield from the commercially available 2,6-dimethoxybenzoic acid by reacting its chloride with dimethyl cadmium, formed *in situ* from methylmagnesium bromide and cadmium chloride.

As has already been mentioned, *p*-anisoyl chloride reacts with 2,6-dihydroxyacetophenone to give 2-(*p*-anisoyloxy)-6-hydroxyacetophenone (V). When this was treated with powdered potassium hydroxide in pyridine, it underwent simultaneous rearrangement and intermolecular acylation, to give 1-[2-(*p*-anisoyloxy)-6-hydroxyphenyl]-3-(*p*-methoxyphenyl)propane-1,3-dione (XVI). The same diketone was also obtained from the diester VI. When XVI was warmed with glacial acid containing a little concentrated sulphuric acid, both hydrolysis and cyclisation took place, affording 5-hydroxy-4-′methoxyflavone (XVII).

This flavone has earlier been obtained in poor yield by fusion of 2,6-dihydroxyacetophenone with *p*-anisic anhydride and sodium anisate [10,15] or by the Baker-Venkataraman rearrangement of 2,6-bis(*p*-anisoyloxy)acetophenone and subsequent cyclisation of the rearrangement products,[13] 3-(*p*-anisoyl)-5-hydroxy-4′-methoxyflavone being the major product.



	R	R′
X	CH_3	NO_2
XIV	CH_3	I
XV	H	I
XVII	H	OCH_3

EXPERIMENTAL

Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared spectra were run on a Perkin-Elmer 237 or 337 spectrophotometer with grating monochromator, using KBr discs. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany. The mass spectra were kindly recorded by Dr. R. Ryhage, Karolinska institutet, Stockholm.

*2,6-Bis(*p*-nitrobenzoyloxy)acetophenone (I) and 2-hydroxy-6-(*p*-nitrobenzoyloxy)acetophenone (II).* 2,6-Dihydroxyacetophenone [16] (15.2 g, 0.1 mole) in redistilled pyridine (40 ml) was treated portionwise with recrystallised *p*-nitrobenzoyl chloride (18.6 g, 0.1 mole). The mixture was heated on a boiling water-bath for 0.5 h, whereafter it was cooled and treated with ethanol. After standing the mixture in the cooler for 1.5 h the crystals were collected, washed with ethanol, and dried, affording a product melting at 194–199°. The yields in three experiments ranged from 11 to 15 g (0.025–0.033 moles; 50–66 %). Recrystallisation from a mixture of ethanol and dioxane gave an analytical sample of I, m.p. 201–203°; ν_{max} 1750 (C=O ester), 1705 cm^{-1} (C=O ketone). (Found: C 58.76; H 3.46; N 6.22. Calc. for $C_{22}H_{14}N_2O_9$: C 58.67; H 3.13; N 6.22).

From the mother liquor was obtained 2.9–8.4 g, (10–28 %) of crude II, m.p. 120–132°. Two recrystallisations from ethanol-dioxane gave an analytical sample melting at 133.5–135.5°; ν_{max} 1750 (C=O ester), 1640 cm^{-1} (C=O chelated ketone). (Found: C 59.88; H 3.75; N 5.27. Calc. for $C_{15}H_{11}NO_6$: C 59.80; H 3.68; N 4.65).

*2,6-Bis(*p*-iodobenzoyloxy)acetophenone (III) and 2-hydroxy-6-(*p*-iodobenzoyloxy)acetophenone (IV).* A mixture of *p*-iodobenzoyl chloride (26.6 g, 0.1 mole) and 2,6-dihydroxyacetophenone (15.2 g, 0.1 mole) was treated with 150 ml of redistilled pyridine. After being shaken at room temperature for 15 min, the thick paste was transferred to an ice-cold solution of 400 ml of 0.5 M hydrochloric acid. The crude product that fell out was collected and fractionally recrystallised from ethanol, giving 19 g (62 %) of crude diester III, m.p. 157–165°, and 8.7 g (24 %) of the crude monoester IV. The diester III was recrystallised twice from an ethanol-dioxane mixture, giving an analytical sample, m.p. 172–174°; ν_{max} 1740 (C=O ester), 1700 cm^{-1} (C=O ketone). (Found: C 43.09; H 2.32; I 41.58. Calc. for $C_{22}H_{14}I_2O_6$: C 43.16; H 2.30; I 41.46.

The monoester IV was repeatedly recrystallised from ethanol-dioxane, giving a white crystalline product, m.p. 140–146°; ν_{max} 1745 (C=O ester), 1635 cm^{-1} (C=O chelated ketone). (Found: C 47.52; H 2.81; Calc. for $C_{15}H_{11}IO_4$: C 47.14; H 2.90).

*2-(*p*-Anisoyloxy)-6-hydroxyacetophenone (V).* *p*-Anisoyl chloride (26.4 g, 0.155 mole) was added portionwise to a solution of 2,6-dihydroxyacetophenone (23.6 g, 0.155 mole) in 60 ml of pyridine. The clear yellow solution was warmed on a water-bath for 0.5 h, cooled, and the pyridine hydrochloride filtered off. The filtrate was evaporated under vacuum and the glass-like viscous residue crystallised from ethanol, yielding 20.6 g (46 %) of white crystals, m.p. 92–102°. Recrystallisation from ethanol gave an analytically pure sample, m.p. 100–103°; ν_{max} 1730 (C=O ester), 1630 cm^{-1} (C=O chelated ketone). (Found: C 67.52; H 4.89. Calc. for $C_{16}H_{14}O_5$: C 67.13; H 4.93).

*2,6-Bis(*p*-anisoyloxy)acetophenone (VI).* This product was obtained in 86 % yield from *p*-anisoyl chloride (11.5 g, 0.066 mole), 2,6-dihydroxyacetophenone (4.6 g, 0.03 mole), and 20 ml of pyridine, the working procedure being essentially similar to that employed in the synthesis of V. Recrystallisation of the crude material, m.p. 138–139°, from ethanol gave white crystals of m.p. 139.5–140.5° (lit.[6] 141°); ν_{max} 1740 (C=O ester), 1700 cm^{-1} (C=O ketone).

*5-Hydroxy-3-(*p*-nitrobenzoyl)-4'-nitroflavone (VII).* The acetophenone derivative I (14.1 g, 0.031 mole) dissolved in 50 ml of redistilled pyridine was treated in one portion with powdered potassium hydroxide (4.5 g, *ca.* 0.07 mole) at about 50°. The dark brown mixture was stirred at that temperature for 30 min, cooled and treated with water. The clear solution was acidified with a slight excess of 10 % acetic acid and the yellow crystalline precipitate collected, washed with water and dried, affording 9 g (67 %) of crude product, m.p. 226–236°. Several recrystallisations from dioxane gave an analytical sample, m.p. 241–242.5°; ν_{max} 1680 (C=O ketone), 1645 cm^{-1} (C=O flavone). (Found: C 61.29; H 2.85; N 6.52. Calc. for $C_{22}H_{12}N_2O_8$: C 61.11; H 2.80; N 6.48).

The same product was obtained in 27 % yield when compound II was treated in essentially the same manner.

2-Methoxy-6-(p-nitrobenzoyloxy)acetophenone (VIII). To a stirred solution of 2-hydroxy-6-methoxyacetophenone [17] (16.6 g; 0.1 mole) in 50 ml of dry pyridine was added portionwise *p*-nitrobenzoyl chloride (18.6 g, 0.1 mole) at room temperature. The reaction mixture was allowed to stand at room temperature overnight, when it was poured into 500 ml of 0.8 M hydrochloric acid. The crystals that fell out were collected, washed with water, with sodium carbonate solution and again with water, then dried, affording 27.2 g (86 %) of white crystals, m.p. 149–150°. Recrystallisation from ethanol gave an analytical sample, m.p. 149.5–150.5°: ν_{max} 1745 (C=O ester), 1685 cm^{-1} (C=O ketone). (Found: C 60.94; H 4.56; N 4.52. Calc. for $C_{16}H_{13}NO_6$: C 60.95; H 4.16; N 4.44).

1-(2-Hydroxy-6-methoxyphenyl)-3-(p-nitrophenyl)propane-1,3-dione (IX). The acetophenone derivative VIII (26 g, 0.083 mole) in 50 ml of dry pyridine was treated in one portion with powdered potassium hydroxide (8.1 g, *ca.* 0.12 mole). The mixture was shaken at room temperature for 15 min, by when it became converted to a brown paste. After being warmed in a water-bath for 15 min, it was treated first with water, and then with 100 ml of 20 % acetic acid. The yellow precipitate was collected, washed and dried, giving 14.7 g (56 %) of crude diketone, m.p. 171–175°. Recrystallisation from ethanol gave bright yellow crystals, m.p. 176.5–178.5°. The infrared spectrum showed a strong and broad band at 1590 cm^{-1} characteristic for 1,3-diketones.[18] (Found: C 60.81; H 4.51; N 4.59; OCH_3 9.85. Calc. for $C_{16}H_{13}NO_6$: C 60.95; H 4.16; N 4.44; OCH_3 9.84).

5-Methoxy-4'-nitroflavone (X). The diketone IX (14.7 g, 0.047 mole) was heated on a water-bath for 1.5 h with 70 ml of glacial acetic acid containing 2.5 ml of concentrated sulphuric acid. After cooling, the product was collected, giving 13.6 g (97 %) of crude flavone, m.p. 267–268°. Recrystallisation from dioxane gave a pale yellow crystalline sample, m.p. 274.5–275.5°; ν_{max} 1640 cm^{-1} (C=O). (Found: C 63.71; H 3.86; OCH_3 10.53. Calc. for $C_{16}H_{11}NO_5$: C 64.64; H 3.73; OCH_3 10.44).

4,4'-Bis(5-methoxy-2-chromonyl)azoxybenzene (XI). The flavone X (6.3 g, 0.021 mole) was added to a mixture made up from 50 ml of ethanol, 10 ml of concentrated ammonia solution and 1 g of a Pd-$CaCO_3$ catalyst, prepared according to Lindlar,[19] except that the poisoning by lead was omitted. After being shaken over hydrogen for 5 h, about two thirds of the theoretical amount of hydrogen had been consumed, and practically no further uptake could be detected. The mixture was filtered, the solid residue taken up in 70 ml of hot pyridine, the catalyst was filtered off and the pyridine solution evaporated to dryness under vacuum. The residual yellow powder was recrystallised several times from dimethyl sulphoxide, giving a small amount of fine golden-brown crystals melting at 324° d; ν_{max} 1660 cm^{-1} (C=O). The mass spectrum showed a small peak for the molecular ion at *m/e* 546. (Found: C 70.13; H 4.02; N 5.14; OCH_3 11.12. Calc. for $C_{32}H_{22}N_2O_7$: C 70.33; H 4.06; N 5.13; OCH_3 11.03).

2-Acetoxy-6-hydroxyacetophenone. A solution of sodium hydroxide (10 g, 0.25 mole) in 50 ml of water was added to a stirred suspension of 2,6-dihydroxyacetophenone (33 g, 0.22 mole) in 50 ml of water whilst a stream of hydrogen was passed through the apparatus. Crushed ice (100 g) was added, followed by addition of acetic anhydride (23 ml, 0.22 mole). The mixture was stirred at room temperature for 1 h when the light-coloured oil that fell out was extracted into benzene. After filtering the extract and drying it over sodium sulphate, the solvent was distilled off. The residual oil was distilled under vacuum, giving 38 g (88 %) of crude product, b.p. 113–135°/0.7 mm Hg. This was redistilled, and a middle fraction, b.p. 116°/1.0 mm Hg, (solidified at room temperature) was drawn off for analysis; ν_{max} 1770 (C=O ester), 1630 cm^{-1} (C=O ketone). (Found: C 61.62; H 5.37. Calc. for $C_{10}H_{10}O_4$: C 61.85; H 5.18).

2-Acetoxy-6-(p-nitrobenzoyloxy)acetophenone (XII). A solution of *p*-nitrobenzoyl chloride (9.3 g, 0.05 mole) in 30 ml of redistilled pyridine was treated with 2-acetoxy-6-hydroxyacetophenone (9.7 g, 0.05 mole) in one portion. The flask was stoppered and shaken vigorously. Reaction was immediate, as evidenced by evolution of heat. After being allowed to stand overnight, the mixture was poured into 400 ml of 0.4 M hydrochloric acid, causing a milky oil to settle out. The supernatant was poured off, the oil was washed several times with water by decantation, then triturated with ethanol. Crystallisation eventually set in, affording 11.8 g (69 %) of a crude product melting at 106–120°. Recrystallisation from absolute ethanol containing 10 % of dioxane gave an analytical sample, m.p. 117.5–120°; ν_{max} 1770 (C=O acetate), 1745 (C=O benzoate), 1695 cm^{-1} (C=O ketone). (Found: C 59.57; H 3.74; N 4.18. Calc. for $C_{17}H_{13}NO_7$: C 59.48; H 3.82; N 4.08).

2,6-Dimethoxyacetophenone. This compound has earlier been prepared either from 2,6-dimethoxybenzonitrile [20] or through methylation of 2,6-dihydroxyacetophenone.[21,22] However, we found that it could be obtained more conveniently in the following way: Methylmagnesium bromide was prepared by dropping a solution of methyl bromide (300 g, 3.15 mole) in 1.5 l of absolute ether onto magnesium (73 g, 3.0 mole). At the end of the reaction, the clear supernatant solution was decanted from the small amount of residual unreacted magnesium, and an aliquot corresponding to 2.1 moles of Grignard reagent was transferred to a 3-necked round-bottomed flask. All these operations were performed under nitrogen.

The stirred ethereal Grignard solution was cooled with a water-bath, when powdered anhydrous cadmium chloride (349 g, 1.91 mole) was added portionwise. Dry benzene (500 ml) was then added, and the reaction mixture warmed in such a way as to permit the bulk of the ether to escape. After refluxing for 45 min, a solution of 2,6-dimethoxybenzoyl chloride [23] (208 g, 1.04 mole) in 500 ml of dry benzene was added slowly to the stirred, refluxing mixture. After refluxing for 1 h and stirring overnight at room temperature, the reaction mixture was decomposed with a concentrated solution of ammonium chloride. The organic phase was removed, dried over sodium sulphate, and fractionated, affording 131.5 g (70 %) of 2,6-dimethoxyacetophenone, b.p. 121—123°/1.5 mm Hg, which set to a solid mass at room temperature.

*1-(2,6-Dimethoxyphenyl)-3-(*p*-iodophenyl)propane-1,3-dione (XIII).* Sodium dust (3.45 g, 0.15 mole) was added to a stirred mixture of ethyl *p*-iodobenzoate (51.8 g, 0.19 mole) and 2,6-dimethoxyacetophenone (18.0 g, 0.1 mole). The mixture was heated in an oil-bath at 150° for 4 h when it was cooled and decomposed with crushed ice. The precipitate that fell out was collected, washed, and dried, affording 16.5 g (40 %) of the crude diketone XIII, m.p. 268—275°. Recrystallisation from ethanol gave an analytical sample of m.p. 276—276.5°. The analytical data are in agreement with a "hydrated" form of the diketone XIII. (Found: C 47.17; H 3.67; I 29.11; OCH_3 14.14. Calc. for $C_{17}H_{17}IO_5$: C 47.68; H 4.00; I 29.64; OCH_3 14.49).

A mixture of the "hydrated" diketone (4.1 g, 0.0096 mole), pyridine hydrochloride (2.3 g, 0.02 mole) and glacial acetic acid (1 ml) was heated in an oil-bath at 150° for 6 h. After cooling, the mixture was treated with water and ethanol, and the product collected, washed, and dried, yielding 3.5 g (85 %) of yellow crystals, m.p. 150—155°. Recrystallisation from ethanol gave pale beige crystals of the title-compound, m.p. 155.5—156.5°; ν_{max} 1595 cm^{-1} (1,3-diketone). (Found: C 50.06; H 3.64. Calc. for $C_{17}H_{15}IO_4$: C 49.77; H 3.69).

4'-Iodo-5-methoxyflavone (XIV). The "hydrated" form of the diketone XIII (4.3 g, 0.01 mole) was heated on a boiling water-bath for 2 h with hydrogen iodide (10 ml, 67 %), the mixture was cooled and poured into a solution of sodium pyrosulphite. The precipitate was collected, giving 2.4 g (63 %) of crude product melting at 202—206°. Two recrystallisations from ethanol gave pale pink crystals of XIV, m.p. 207.5—209°; ν_{max} 1640 cm^{-1} (C=O); *m/e* 378 (molecular ion). (Found: C 50.85; H 3.19; I 33.78; OCH_3 8.47. Calc. for $C_{16}H_{11}IO_3$: C 50.81; H 2.93; I 33.56; OCH_3 8.21).

5-Hydroxy-4'-iodoflavone (XV). The flavone XIV (1.4 g, 0.0037 mole) was heated at 130—140° with 50 ml of 67 % hydrogen iodide for 3.5 h. After working up as above, there was obtained 1.26 g (93 %) of crude 5-hydroxy-4'-iodoflavone, m.p. 189—197°. Recrystallisation from ethanol-dioxane gave an analytically pure sample melting at 201—202°; ν_{max} 1640 cm^{-1} (C=O); *m/e* 364 (molecular ion). (Found: C 49.65; H 2.59; I 34.95. Calc. for $C_{15}H_9IO_3$: C 49.47; H 2.49; I 34.85).

The same product was obtained in 69 % yield directly from the hydrated diketone XIII, the experimental procedure being essentially the same as employed above.

*1-[2-(*p*-Anisoyloxy)-6-hydroxyphenyl]-3-(*p*-methoxyphenyl)propane-1,3-dione (XVI).* A mixture consisting of the diester VI (8.8 g, 0.02 mole), powdered potassium hydroxide (1.8 g, *ca.* 0.028 mole), and pyridine (25 ml) was shaken at room temperature for 10 min, then heated on a water-bath for 10 min. Cooling and acidification with dilute acetic acid gave 5 g (57 %) of the crude diketone, m.p. 152—155°. Several recrystallisations from ethanol gave fine, bright-yellow hair-like crystals, m.p. 159—160.5°; ν_{max} 1750 (C=O ester), 1620 cm^{-1} (1,3-diketone). (Found: C 68.92; H 4.58. Calc. for $C_{24}H_{20}O_7$: C 68.56; H 4.80).

The same product was obtained in small yield when the monoester V was treated with potassium hydroxide and pyridine in the same manner.

5-Hydroxy-4'-methoxyflavone (XVII). When the diketone XVI (3.0 g. 0.007 mole) was heated on a boiling water-bath for 0.5 h with 20 ml of glacial acetic acid and 2 ml of concentrated sulphuric acid, 1.3 g (72 %) of a powdery grey product melting at 140—150° was obtained. Several recrystallisations from ethyl acetate gave fine, pale-yellow hair-like crystals of the flavone XVII, m.p. 153—154.5°, lit. [15] 155—156°; ν_{max} 1660 cm^{-1} (C=O). The compound gave a correct elemental analysis for $C_{16}H_{12}O_4$.

REFERENCES

1. Gottlieb, B. *Anat. Anz.* **46** (1914) 179.
2. Schour, I., Hoffman, M. M., Sarnat, B. G. and Engel, M. B. *J. Dental Res.* **20** (1941) 411.
3. Schorr, S., Aviad, I. and Laufer, A. *Radiology* **73** (1959) 410.
4. Milch, R. A., Rall, D. P. and Tobie, J. E. *J. Natl. Cancer Inst.* **19** (1957) 87.
5. Milch, R. A., Rall, D. P. and Tobie, J. E. *J. Bone Joint Surg.* **A 40** (1958) 897.
6. Baker, W. and Flemons, G. F. *J. Chem. Soc.* **1948** 2138.
7. Allan, J. and Robinson, R. *J. Chem. Soc.* **125** (1924) 2192.
8. Anderson, J. A. *Can. J. Research* **7** (1932) 285.
9. Baker, W. *J. Chem. Soc* **1933** 1381.
10. Baker, W., Flemons, G. F. and Winter, R. *J. Chem. Soc.* **1949** 1560.
11. Baker, W. *J. Chem. Soc.* **1934** 1953.
12. O'Toole, T. M. and Wheeler, T. S. *J. Chem. Soc.* **1956** 4411.
13. Looker, J. H. and Hanneman, W. W. *J. Org. Chem.* **27** (1962) 3261.
14. Rama Rao, A. V., Telang, S. A. and Madhavan Nair, P. *Indian J. Chem.* **2** (1964) 431.
15. Syed, I. Z. and Wheeler, T. S. *J. Chem. Soc.* **1936** 1714.
16. Russel, A. and Frye, J. R. *Org. Syn. Coll. Vol.* **3** (1960) 281.
17. Baker, W. *J. Chem. Soc.* **1939** 956.
18. Rasmussen, R. S., Tunnicliff, D. D. and Brattain, R. R. *J. Am. Chem. Soc.* **71** (1949) 1068.
19. Lindlar, H. *Helv. Chim. Acta* **35** (1952) 446.
20. Mauthner, F. *J. prakt. Chem.* [2] **139** (1934) 290.
21. Limaye, D. M. and Gangal, D. D. *Rasayanam* **1** (1936) 64; *Chem. Abstr.* **31** (1937) 2182.
22. Shamshurin, A. A. *J. Gen. Chem. USSR* **16** (1946) 99.
23. Abraham, E. P. and Newton, G. G. F. Brit. Pat. 953696 (1964).

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