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Cyclisation of 2,3-Dimethoxy-β-phenoxycinnamic Acid to Indone and Flavone Derivatives

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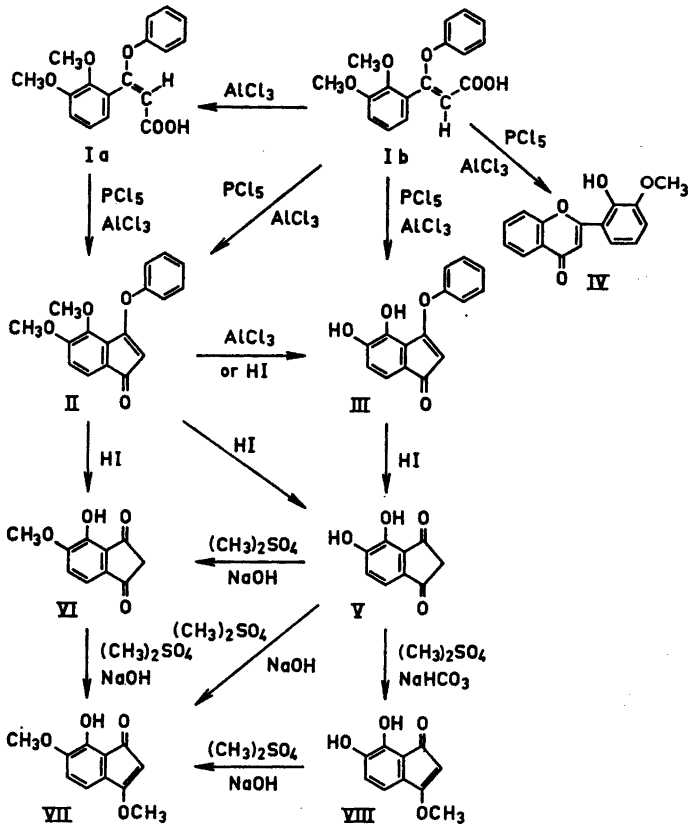
Ring-closure of the high-melting geometric isomer of 2,3-dimethoxy-β-phenoxycinnamic acid (Ia) gives 4,5-dimethoxy-3-phenoxyindone. The low-melting isomer (Ib) gives in addition 2′-hydroxy-3′-methoxyflavone. These results show that the carboxyl and the phenoxy groups occupy *trans* positions in Ia and *cis* in Ib. The *cis* isomer can be easily isomerised to the *trans* form with aluminium chloride.

Methylation of 4,5-dihydroxy-1,3-indandione gives, according to the experimental conditions, 4-hydroxy-5-methoxy-1,3-indandione, 6,7-dihydroxy-3-methoxyindone, and 3,6-dimethoxy-7-hydroxyindone.

In the attempted synthesis of 2′,3′-dimethoxyflavone through cyclisation of 2,3-dimethoxy-β-phenoxycinnamic acid, Ruhemann [1] successively treated the acid with thionyl chloride and aluminium chloride. However, instead of the expected flavone, the isolated product was found to be 4,5-dimethoxy-3-phenoxyindone which on treatment with hydriodic acid yielded 4,5-dihydroxy-1,3-indandione. The indone derivative was obtained with either of the two geometric isomers of the acid, as well as with a mixture of both.

Since we required 4,5-dihydroxy-1,3-indandione as starting material for a series of syntheses, we decided to prepare it according to the method of Ruhemann. We found, however, that the ring-closure of the cinnamic acid derivative did not proceed quite as simply as described by Ruhemann, and we therefore undertook a somewhat closer investigation of the cyclisation reaction.

The two isomeric 2,3-dimethoxy-β-phenoxycinnamic acids were subjected to the cyclisation procedure under identical experimental conditions. It was found that the high-melting isomer (Ia) afforded 4,5-dimethoxy-3-phenoxyindone (II) in good yield, whereas the low-melting isomer (Ib) yielded in addition a product which gave a correct analysis for a hydroxymethoxyflavone (IV). That IV was indeed a hydroxymethoxyflavone was further confirmed by its methylation to 2′,3′-dimethoxyflavone, and demethylation to 2′,3′-dihydroxyflavone, both of which have been described.[2] The positions of the



Scheme 1

hydroxyl and methoxy groups were subsequently established by the synthesis of 2′-hydroxy-3′-methoxyflavone, which was identical with compound IV formed in the ring-closure experiments.

Besides 4,5-dimethoxy-3-phenoxyindone and 2′-hydroxy-3′-methoxyflavone, a third compound was sometimes isolated in the ring-closure of Ib; it yielded 4,5-dihydroxy-1,3-indandione (V) on treatment with hydriodic acid, and gave a correct analysis for 4,5-dihydroxy-3-phenoxyindone (III). Although 4,5-dimethoxy-3-phenoxyindone did not undergo demethylation when treated with excess of aluminium chloride under the conditions prevailing in the cyclisation experiments, and required refluxing in benzene before demethylation to III was complete, it could nevertheless be quite possible that demethylation of the initially formed indone (II) occurred through local overheating. However, the possibility that the chloride of the acid Ib suffered demethylation before ring-closure should not be overlooked, especially in view of the fact that the indone derivative II obtained from the high-melting acid Ia never underwent demethylation to III in the ring-closure experiments.

The fact that the high-melting isomer Ia gave rise to indone derivative only, and the low-melting isomer Ib yielded a flavone as well, makes it justified in assigning to Ia that configuration which has the carboxyl group in close proximity to the dimethoxyphenyl group, and to Ib the configuration having the carboxyl group adjacent to the phenoxy group. The isomer Ia will thus be designated as the *trans* and Ib as the *cis* isomer, referring to the relative positions of the phenoxy and carboxyl groups. That Ib gives rise not only to a flavone, as would be expected, but also cyclises to indone derivatives, is easily explained on the basis of its facile isomerisation to Ia. The isomer Ia is apparently the more stable, since it was formed in good yield when Ib was treated with aluminium chloride in benzene at room temperature, whilst no change was observed when Ia was treated similarly.

Since the only flavone ever isolated in our experiments was the 2′-hydroxy-3′-methoxy derivative, and never the expected 2′,3′-dimethoxyflavone, experiments were made to ascertain if the latter could be demethylated during cyclisation; the results showed that 2′,3′-dimethoxyflavone could be quantitatively demethylated to IV with aluminium chloride at room temperature. However, as mentioned above, demethylation of the chloride of Ib should not be ruled out.

In an attempt to increase the yield of indone derivatives through excluding the possibility of flavone formation, 2,3-dimethoxy-β-ethoxycinnamic acid was prepared and subjected to cyclisation experiments. However, all attempts at ring-closure were unsuccessful. A possible explanation for this failure might be that the cinnamic acid derivative obtained was the isomer having the carboxyl group *trans* to the dimethoxyphenyl group, and if this isomer is more stable than the *cis* form, isomerisation followed by ring-closure will not occur.

Treatment of 4,5-dimethoxy-3-phenoxyindone (II) with seven equivalents of 67 % hydriodic acid yielded 4,5-dihydroxy-1,3-indandione (V) in good yield. When a smaller excess of hydriodic acid was used, we were also able to isolate from the reaction mixture 4,5-dihydroxy-3-phenoxyindone (III), in addition to a new compound which gave a correct analysis for a hydroxymethoxyindandione, and whose infrared spectrum * indicated the presence of a strong intramolecular hydrogen bond. The identical compound was also obtained by treating 4,5-dihydroxy-1,3-indandione (V) with little more than one equivalent of dimethyl sulphate in aqueous acetone in the presence of sodium hydroxide. The methoxy group must obviously occupy either the 4- or the 5-position in this indandione derivative. However, since the spectrum indicates a hydroxyl group *peri* to a carbonyl group and since it is known that phenolic hydroxyl groups *peri* to carbonyl groups are resistant to methylation because of hydrogen-bonding, we consider the new compound to be 4-hydroxy-5-methoxy-1,3-indandione (VI).

Additional support for this structure-assignation is given by its behaviour towards phenylhydrazine. When treated with excess of phenylhydrazine, VI

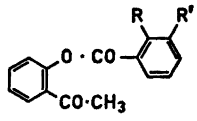
* Infrared spectra were recorded in potassium bromide discs, since the compounds were generally insufficiently soluble in all suitable solvents, precluding a closer study of hydrogen-bonding.

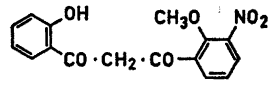
gave a monophenylhydrazone, in contrast to the bisphenylhydrazone obtained by us from 4,5-dimethoxy-1,3-indandione, and by Wislicenus and Kötzle [3] from 1,3-indandione. 4,5-Dihydroxy-1,3-indandione, which has a hydrogen-bonded carbonyl group, also gave only a monophenylhydrazone, hence the failure of VI to give a bisphenylhydrazone could be attributed to the unreactivity of one of the carbonyl groups due to its participation in a hydrogen bond with a neighbouring hydroxyl group, indicating VI to be 4-hydroxy-5-methoxy-1,3-indandione.

Methylation of VI with dimethyl sulphate gave a compound which was identical with the product obtained when 4,5-dihydroxy-1,3-indandione (V) was treated with excess of dimethyl sulphate in aqueous acetone in the presence of sodium hydroxide. Methoxyl determination and NMR-spectrum (sharp methyl signals at τ 6.12 and 5.98) showed this compound to be a dimethoxy derivative. This was not identical with 4,5-dimethoxy-1,3-indandione, described by Landau [4] and prepared by us for comparison. The new dimethoxy compound can thus be only either 3,5-dimethoxy-4-hydroxyindone, or the isomeric 3,6-dimethoxy-7-hydroxyindone (VII). However, since the compound failed to give a derivative with phenylhydrazine, we consider it to be 3,6-dimethoxy-7-hydroxyindone (VII), obtained from the enol forms of V or VI.

When 4,5-dihydroxy-1,3-indandione was treated with dimethyl sulphate in anhydrous acetone, using sodium bicarbonate instead of sodium hydroxide, a monomethoxy derivative which was not identical with 4-hydroxy-5-methoxy-1,3-indandione (VI) was obtained in good yield. Since this new compound failed to give a phenylhydrazone, and since it could be further alkylated to 3,6-dimethoxy-7-hydroxyindone (VII), we consider it to be 6,7-dihydroxy-3-methoxyindone (VIII). This selective methylation depending on the experimental conditions might be associated with different acidities of the enolic and phenolic hydroxyl groups. It would seem that the bicarbonate ion is too weak a base to give an anion with a phenolic hydroxyl group but is sufficiently strong to ionise the more acidic enolic group, giving the enol ether on alkylation. In the presence of sodium hydroxide, however, both types of hydroxyl groups are ionised, but since the phenoxide ion is probably more nucleophilic, it reacts more rapidly, giving predominantly phenol ether when only one equivalent of dimethyl sulphate is used. Similar selective methylation depending on differing acidities of hydroxyl groups has been reported [5] in the flavone series.

In order to identify the unknown hydroxymethoxyflavone IV, 2′-hydroxy-3′-methoxyflavone was synthesised unambiguously in two independent ways, and found to be identical with IV. In one method 2,2′-dihydroxy-3-methoxychalcone (IX) was subjected to oxidative cyclisation with selenium dioxide, giving IV in small yield. In the second method, it was intended to convert *o*-(2-acetoxy-3-methoxybenzoyloxy)-acetophenone (XI) to 1-(2-acetoxy-3-methoxyphenyl)-3-(2-hydroxyphenyl)-propane-1,3-dione through the Baker-Venkataraman transformation, and to cyclise the diketone to the corresponding flavone. However, it was found that under the conditions intended to lead to the transformation, cyclisation with simultaneous deacetylation had taken place as well, leading directly to the flavone IV.

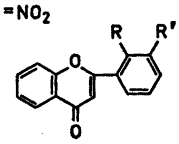




XI R = O·CO·CH$_3$, R' = OCH$_3$

XIII R = OCH$_3$, R' = NO$_2$

XIV



IV R = OH, R' = OCH$_3$

XV R = OH, R' = NO$_2$

XVI R = OCH$_3$, R' = NO$_2$

XVII R = OCH$_3$, R' = NH$_2$

Attempts to synthesise the isomeric 3'-hydroxy-2'-methoxyflavone by replacement of the amino group in 3'-amino-2'-methoxyflavone (XVII) with a hydroxyl group *via* the diazonium intermediate were unsuccessful. The flavone XVII was prepared in the following way: *o*-(2-methoxy-3-nitrobenzoyloxy)-acetophenone (XIII) was converted with potassium hydroxide in pyridine (Baker-Venkataraman transformation) at 50—60° to 1-(2-hydroxyphenyl)-3-(2-methoxy-3-nitrophenyl)-propane-1,3-dione (XIV), which was cyclised to 2'-methoxy-3'-nitroflavone (XVI). Catalytic reduction afforded the flavone XVII.

When the Baker-Venkataraman transformation was carried out at 85°, ring-closure with simultaneous demethylation to 2'-hydroxy-3'-nitroflavone (XV) occurred.

EXPERIMENTAL

Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared spectra were run on a Perkin-Elmer 237 spectrophotometer with grating monochromator using KBr discs. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany.

2,3-Dimethoxy-β-phenoxycinnamic acid (I). 2,3-Dimethoxyphenylpropiolic acid [6] was converted to a mixture of the isomeric 2,3-dimethoxy-β-phenoxycinnamic acids by the method of Ruhemann.[1]

The crude acid mixture could be separated into its geometric isomers by fractional crystallisation from ethanol, the high-melting isomer (Ia), m.p. 192—193°, being much less soluble than the low-melting isomer (Ib), m.p. 137—138°.

Ring-closure of 2,3-dimethoxy-β-phenoxycinnamic acid (I): 4,5-Dimethoxy-3-phenoxyindone (II), 4,5-dihydroxy-3-phenoxyindone (III) and 2'-hydroxy-3'-methoxyflavone (IV). The following procedure was generally adopted in the ring-closure of I. The cinnamic acid derivative was suspended in benzene to give a 20—40 % suspension, a 10 % excess of phosphorus pentachloride was added and the stirred mixture warmed on a water-bath for some minutes, until a clear dark-coloured solution was obtained. The reaction mixture was then cooled with an ice-bath and aluminium chloride (5—6 equiv.) was added portion-wise. After stirring the mixture for about 20 min, it was poured onto crushed ice, the precipitate collected, washed with sodium carbonate solution and with water, and dried.

When starting material which consisted predominantly of the high-melting isomer Ia was used, yields of 88–91 % of fairly pure 4,5-dimethoxy-3-phenoxyindone (II), m.p. 180–195°, were obtained. The purified product had m.p. 198–200° (Ref. 1, 199–200°).

The low-melting isomer Ib afforded products of m.p. 165–175° in 70–80 % yield, which proved to be II contaminated with considerable quantities of 2′-hydroxy-3′-methoxyflavone (IV). The mixture was separated into its components by a tedious process involving leaching out of II with hot benzene and of IV with hot dioxane. A 22 % yield of pure II, m.p. 198–200°, was obtained in this way, together with 19 % yield of a compound melting at 204–206°. Recrystallisation from ethanol containing little dioxane gave a pure compound, m.p. 208–209.5°, which gave a correct analysis for 2′-hydroxy-3′-methoxyflavone (IV). The infrared spectrum showed bands at 3400–2400 (OH), and 1630 cm^{-1} (C=O). (Found: C 72.11; H 4.47; OCH_3 11.52. Calc. for $C_{16}H_{12}O_4$: C 71.63; H 4.51; OCH_3 11.57).

The compound IV was identified as 2′-hydroxy-3′-methoxyflavone by comparison with an authentic sample prepared as described below.

In a number of experiments carried out with Ib, a product-mixture was obtained, which consisted mainly of 4,5-dihydroxy-3-phenoxyindone (III), contaminated with lesser amounts of II and IV. This happened especially when the Friedel-Crafts reaction was carried out in too concentrated solutions, when the mixture was not cooled adequately during addition of aluminium chloride, or when the benzenic solution of the acid chloride was added to the aluminium chloride in benzene, instead of *vice versa*. Recrystallisation of this product-mixture from ethanol containing little dioxane gave shiny platelets of 4,5-dihydroxy-3-phenoxyindone (III), m.p. 250–252°. The infrared spectrum showed bands at 3335 (OH), 1710, 1690 (C=O, split), and 1630 cm^{-1} (conjugated C=C). (Found: C 71.36; H 3.92. Calc. for $C_{15}H_{10}O_4$: C 70.86; H 3.96).

This product was also obtained in 84 % yield when 4,5-dimethoxy-3-phenoxyindone (II) was warmed on a water-bath for 20 min with 5 equiv. of aluminium chloride in benzene. When warmed with excess of 67 % HI, III yielded 4,5-dihydroxy-1,3-indandione [1] (V) in 92 % yield.

Cis-trans *isomerisation of Ib to Ia.* When the acid Ib was treated with 3 equiv. of aluminium chloride in benzene for 20 min at room temperature, 48 % of the *trans* isomer, m.p. 190–193°, was obtained after recrystallisation of the crude reaction product.

When the *trans* isomer Ia was treated in a similar manner, most of the starting material was recovered unchanged.

2,3-Dimethoxy-β-ethoxycinnamic acid. To a stirred ethanolic solution of sodium ethoxide, obtained by adding 11.5 g (0.5 mole) of sodium to 150 ml of absolute ethanol, was added dropwise 135 g (0.5 mole) of ethyl 2,3-dimethoxy-β-chlorocinnamate.[1] After the strong exothermic reaction had subsided, the solution was refluxed for 3 h. The cooled solution was then acidified with N H_2SO_4, and the reddish oil that fell out was extracted into ether. After washing and drying the ethereal solution, the solvent was removed under vacuum, leaving a red-coloured oily residue weighing 110 g.

This crude oil was refluxed for one hour with a 10 % excess of 3 N ethanolic KOH, after which the ethanol was removed under vacuum. The residue was dissolved in about 0.5 l of water, the aqueous solution washed with ether, cooled and acidified with 5 N HCl. The viscous yellow oil that settled out was worked up, affording 73 g (73 %) of crude material of indefinite melting point, assumed to be a mixture of the isomeric acids. Two recrystallisations from ethanol gave an analytical sample, m.p. 145–146°. The infrared spectrum showed bands at 3300–2300 (OH), 1695, 1660 (C=O, split), and 1615 cm^{-1} (C=C). (Found: C 61.06; H 6.35. Calc. for $C_{13}H_{16}O_5$: C 61.89; H 6.39).

Attempted ring-closure of this compound did not afford the desired 4,5-dimethoxy-3-ethoxyindone.

Hydriodic acid treatment of 4,5-dimethoxy-3-phenoxyindone (II): 4,5-Dihydroxy-1,3-indandione (V), 4-hydroxy-5-methoxy-1,3-indandione (VI) and 4,5-dihydroxy-3-phenoxyindone (III). The indone derivative II (56.4 g, 0.2 mole) was treated with 140 ml (*ca.* 7 equiv.) of 67 % HI, *d* 1.96, and the mixture warmed on a water-bath for 30 min. The clear homogeneous dark-coloured solution was cooled, poured into 250 ml of water, filtered, and the precipitate washed thorougly with water. The product thus obtained was stirred with 300 ml of N NaOH, the small amount of undissolved matter filtered off,

and the solution acidified with 100 ml of 5 N HCl. The product was collected, washed with water, and vacuum-dried, yielding 31.5 g (91 %) of a whitish powder, m.p. 255–258°. Recrystallisation from aqueous ethanol gave 4,5-dihydroxy-1,3-indandione (V), m.p. 270–272° (Ref. 1, 277–278°). The infrared spectrum showed bands at 3500–2500 (OH), 1725, 1715, and 1695 cm^{-1} (C=O).

In an experiment where the ratio of the indone II to hydriodic acid was 1:4.5, no clear solution was obtained, and the isolated product consisted of a mixture of starting material II, 4,5-dihydroxy-3-phenoxyindone (III), 4,5-dihydroxy-1,3-indandione (V) and a fourth hitherto unknown component. After repeated recrystallisations from ethanol, this last product was obtained as a cream-coloured compound, m.p. 246–247.5°, which gave a correct analysis for 4-hydroxy-5-methoxy-1,3-indandione. The infrared spectrum showed bands at 3300–2300 (OH), and 1710–1660 (non-resolved C=O), 1245, and 1060 cm^{-1} (=C–O–C). (Found: C 62.60; H 4.25; OCH_3 15.69. Calc. for $C_{10}H_8O_4$: C 62.50; H 4.20; OCH_3 16.14).

Phenylhydrazone of 4-hydroxy-5-methoxy-1,3-indandione. The indandione derivative VI (0.96 g, 0.005 mole) was dissolved in 10 ml of hot ethanol and treated with 15 ml (*ca.* 0.01 mole) of a phenylhydrazine reagent, prepared by dissolving 25 ml of redistilled phenylhydrazine in 250 ml of 10 % acetic acid. The clear solution was warmed on a water-bath for 15–20 min, the mixture cooled, and the crystalline product collected. Recrystallisation from ethanol afforded the monophenylhydrazone, m.p. 183–184°. (Found: C 68.06; H 5.12; N 10.10. Calc. for $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.93).

Phenylhydrazone of 4,5-dihydroxy-1,3-indandione. This was prepared as above from V. Crystallisation from ethanol afforded yellow crystals of the monophenylhydrazone, m.p. 187–188°. (Found: C 66.74; H 4.64; N 10.52. Calc. for $C_{15}H_{12}N_2O_3$: C 67.15; H 4.51; N 10.44).

Bisphenylhydrazone of 4,5-dimethoxy-1,3-indandione. When 4,5-dimethoxy-1,3-indandione, prepared by a modification of the method of Landau,[4] was treated with phenylhydrazine reagent as above, a product was obtained which, after recrystallisation from ethanol-dioxane, gave purple-brown flaky crystals of the bisphenylhydrazone, m.p. 182°. (Found: C 71.85; H 5.87; N 14.10. Calc. for $C_{23}H_{22}N_4O_2$: C 71.48; H 5.74; N 14.50).

Methylation of 4,5-dihydroxy-1,3-indandione (V). A. 4-Hydroxy-5-methoxy-1,3-indandione (VI). The dihydroxyindandione V (7.12 g, 0.04 mole) was dissolved in 24 ml of 5 N NaOH (0.12 mole), and to the clear solution was added 24 ml of water and 25 ml of acetone. The mixture was treated dropwise at room temperature with 5 ml (0.054 mole) of dimethyl sulphate, then stirred at 45–55° for 1.5 h. The cooled solution was acidified with 5 N hydrochloric acid and the voluminous precipitate collected. This was taken up in ethanol, the mixture filtered, and the solution evaporated under vacuum to dryness, yielding 7.3 g of crude product. Two recrystallisations from ethanol afforded a pure sample, m.p. 245–247°, which was found by IR-spectrum and mixed m.p. to be identical to the 4-hydroxy-5-methoxy-1,3-indandione (VI) obtained by the hydriodic acid treatment of 4,5-dimethoxy-3-phenoxyindone (II).

B. 6,7-Dihydroxy-3-methoxyindone (VIII). The dihydroxyindandione V (3.6 g, 0.02 mole) was suspended in 70 ml of acetone, and the stirred mixture treated with 5.04 g (0.06 mole) of sodium bicarbonate and 3.7 ml (0.04 mole) of dimethyl sulphate. The mixture was heated under reflux for 5 h, then stirred at room temperature overnight. The insoluble precipitate was collected, taken up in water and acidified with dilute hydrochloric acid. The undissolved product was collected and dried, affording 2.1 g (55%) of a whitish product, m.p. 220–228°. From the original filtrate was obtained a further 1.1 g (29 %) of a somewhat less pure product, m.p. 205–213°. Recrystallisation from ethanol gave pure stout yellow needles of VIII, m.p. 232.5–234.5°. The infrared spectrum showed bands at 3400–2500 (OH), 1710 sh, 1675 (C=O), 1620 (conj. C=C), 1235, and 1035 cm^{-1} (=C–O–C). (Found: C 62.25; H 4.28; OCH_3 15.90. Calc. for $C_{10}H_8O_4$: C 62.50; H 4.20; OCH_3 16.14).

Small amounts of VIII were also obtained in the form of a crystalline modification consisting of long white hair-like needles, m.p. 221.5–230.5° (slow melting), when V was methylated in aqueous acetone using sodium hydroxide, as described in section *A* above.

C. 3,6-Dimethoxy-7-hydroxyindone (VII). The dihydroxyindandione V (8.9 g, 0.05 mole) was dissolved in 30 ml (0.15 mole) of 5 N NaOH, 30 ml of acetone was added, followed by addition of 18 ml (0.2 mole) of dimethyl sulphate to the stirred solution at room temperature. The reaction mixture warmed up spontaneously and after about 5 min, the clear solution was suddenly transformed into a thick pasty mass. The mixture was stirred at room temperature overnight, and the product collected, affording 9.0 g (87 %) of a white powder, m.p. 158–160°. Recrystallisation from ethanol gave pure cream-coloured micro needles, m.p. 177–178.5°. The infrared spectrum showed bands at 3600–3300 (OH), 1725, 1710 (C=O, split), 1620 (conj. C=C), 1240, and 1070 cm^{-1} (=C–O–C). (Found: C 63.95; H 4.86; OCH_3 29.54. Calc. for $C_{11}H_{10}O_4$: C 64.07; H 4.89; OCH_3 30.08).

The same compound was also formed when the indandione VI was shaken at room temperature for 24 h in aqueous acetone with 3 equiv. of 5 N NaOH and 3 equiv. of dimethyl sulphate.

Methylation of VIII in aqueous acetone with 3 equiv. of dimethyl sulphate and 3 equiv. of 5 N NaOH likewise gave VII.

Synthesis of 2'-hydroxy-3'-methoxyflavone (IV). Method 1. 2,2'-Dihydroxy-3-methoxychalcone (IX) was prepared by refluxing a mixture of *o*-vanillin (30.4 g, 0.2 mole), *o*-hydroxyacetophenone (30 ml, 0.025 mole), piperidine (5 ml), and glacial acetic acid (1 ml) in 100 ml of absolute ethanol for 4.5 h. After allowing the mixture to stand at room temperature overnight, 28 g (52 %) of orange crystals, m.p. 179–181°, were collected. Recrystallisation from ethanol gave an analytically pure sample of the chalcone IX, m.p. 183.5–184.5°. The infrared spectrum showed bands at 3400 sh, 3330 (OH), 1630 (C=O), and 1610 cm^{-1} (conj. C=C). (Found: C 71.22; H 5.01; OCH_3 11.60. Calc. for $C_{16}H_{14}O_4$: C 71.10; H 5.22; OCH_3 11.48).

Ring-closure to IV. The chalcone IX (8.1 g, 0.03 mole) was dissolved in 100 ml of amyl alcohol, 8.1 g of selenium dioxide was added and the mixture refluxed for 13 h in an oil-bath maintained at 150°. The mixture was filtered to remove selenium, and the solvent removed by steam distillation. The supernatant water was poured off, and the semi-solid residue taken up in hot ethanol. After cooling, 1.1 g (14 %) of a light-brown product, m.p. 200–203°, was collected. Recrystallisation from ethanol-dioxane gave a product melting at 204–206°. Mixed m.p. and IR-spectrum showed this to be identical to compound IV obtained in the ring-closure of Ib, proving IV to be 2'-hydroxy-3'-methoxyflavone.

Method 2. 2-Acetoxy-3-methoxybenzoic acid (X). 2-Hydroxy-3-methoxybenzoic acid [7] (38.5 g, 0.23 mole) was warmed with acetyl chloride (45 ml, 0.64 mole) and pyridine (1 ml) on a water-bath in such a way as to permit the excess acetyl chloride to distill slowly, the last remnants being removed under vacuum. Toluene was then added to the dark oily residue and removed under vacuum, affording a dirty-coloured solid residue. This was taken up in 70 ml of hot ethanol, the solution decolourised with active carbon, and the filtered solution chilled, whereupon 32 g (66 %) of crude product, m.p. 127–132°, were collected. Recrystallisation from benzene gave a pure product, m.p. 138.5–140°. The infrared spectrum showed bands at 3300–2300 (OH), 1765 (ester C=O), 1705, and 1690 cm^{-1} (carboxyl C=O, split). (Found: C 57.25; H 4.65. Calc. for $C_{10}H_{10}O_5$: C 57.14; H 4.80).

o-(2-Acetoxy-3-methoxybenzoyloxy)-acetophenone (XI). The acid X was gently refluxed for 2 h with 3 equiv. of redistilled thionyl chloride, excess of which was then removed under vacuum. The resulting crude product was added to a solution of 1 equiv. (0.05 mole) of *o*-hydroxyacetophenone in 20 ml of dry pyridine. The mixture warmed up spontaneously and a crystalline precipitate fell out shortly after. The mixture was allowed to stand at room temperature for 45 min, when it was poured into 600 ml of 3 % HCl containing 200 g of crushed ice. The supernatant liquid was poured off, the viscous oily residue was washed several times with water by decantation and then taken up in ethanol. The ethanolic solution was allowed to stand overnight in an evacuated desiccator, the resulting crystalline precipitate was collected, suspended in ether, filtered, and dried, affording 8.9 g (54 %) of crude product, m.p. 95–107°. Crystallisation first from methanol and then from absolute ethanol gave a pure product, m.p. 113.5–115.5°. The infrared spectrum had bands at 1765, 1740 (ester C=O), and 1690 cm^{-1} (ketone C=O). (Found: C 65.74; H 4.91; OCH_3 10.04. Calc. for $C_{18}H_{16}O_6$: C 65.85; H 4.91; OCH_3 9.45).

Ring-closure to IV. The ester XI (3.77 g, 0.011 mole) was dissolved in 50 ml of dry pyridine, the solution warmed to 65° and treated in one portion under vigorous stirring with 2.5 g (0.044 mole) of 85 % finely-powdered KOH. After a short while, a copious orange precipitate was formed. Stirring was continued at 65—75° for 0.5 h, the mixture was allowed to cool and then treated with 200 ml of 10 % acetic acid; a yellow crystalline precipitate (1.84 g) was collected, m.p. 190—210°. After several crystallisations, pale-yellow hair-like crystals, m.p. 201—205°, were obtained. Mixed m.p. and IR-spectrum showed this product to be identical to the flavone IV obtained above.

2',3'-Dimethoxyflavone. 2'-Hydroxy-3'-methoxyflavone (IV) (5.4 g, 0.02 mole) was suspended in 16 ml (0.04 mole) of 2.5 N NaOH, 20 ml of ethanol was added, followed by addition of 3.7 ml (0.04 mole) of dimethyl sulphate to the stirred orange-coloured paste. The mixture was stirred on a water-bath for 1 h, by when a clear, red-coloured solution was obtained. A further 8 ml of 2.5 N NaOH was added followed by 3.7 ml of dimethyl sulphate, and the stirred mixture warmed for 45 min more. More dimethyl sulphate (7.4 ml) and 2.5 N NaOH (till the mixture was alkaline) was added, the solution warmed for 45 min, then stirred at room temperature overnight. The pink-coloured precipitate was collected, washed with water, 5 N HCl, water, and dried, affording 5.3 g (95 %) of a pale-yellow product, m.p. 86—88°. Recrystallisation from benzene gave stout yellow crystals, m.p. 72—76° (rapid heating). (Found: C 72.57; H 5.07; OCH_3 21.80. Calc. for $C_{17}H_{14}O_4$: C 72.33; H 5.00; OCH_3 22.00).

This compound exhibits dimorphism. When recrystallised from aqueous ethanol, white micro crystals of m.p. 85—87° were obtained. When the yellow crystalline modification was maintained for a prolonged period at 70—75°, it became converted to the white modification, m.p. 87.5—88.8°.

This compound has been synthesised by Arcoleo *et al.*[2] through ring-closure and subsequent oxidation of 2,3-dimethoxy-2'-hydroxychalcone; they report m.p. 92—93°.

Demethylation of 2',3'-dimethoxyflavone. To a suspension of 2',3'-dimethoxyflavone (1.4 g, 0.005 mole) in 7.5 ml of benzene was added aluminium chloride (3.3 g, 0.025 mole) in one portion and the mixture stood at room temperature for 30 min with occasional shaking. The reaction mixture was hydrolysed with ice-water and filtered, affording 1.31 g (93 %) of a pale yellow product melting at 204—206°. Mixed m.p. determination showed it to be 2'-hydroxy-3'-methoxyflavone. When this was warmed for 30 min with excess of 67 % HI on a water-bath, 2',3'-dihydroxyflavone, m.p. 247.5—251.5° (Ref. 2, 246°) was obtained. The infrared spectrum showed bands at 3420, 3300—3000 (OH), and 1610 cm^{-1} (C=O).

Synthesis of 3'-amino-2'-methoxyflavone (XVII). 2-Methoxy-3-nitrobenzoylchloride (XII). 2-Methoxy-3-nitrobenzoic acid [8] was gently refluxed for 2.5 h with 5 equiv. of thionyl chloride. The excess reagent was removed under vacuum and the residual brown oil cooled, whereupon it solidified. The crystals were ground with petroleum ether and collected, affording a light-brown crystalline product in 84—98 % yield, m.p. 64—67°. Recrystallisation from benzene-petroleum ether afforded brown-pink crystals of the acid chloride, m.p. 67.5—68.7°. The infrared spectrum showed bands at 1750 (C=O), 1530, and 1365 cm^{-1} (NO_2). (Found: C 45.24; H 3.27; N 6.53. Calc. for $C_8H_6ClNO_4$: C 44.56; H 2.81; N 6.50).

o-(2-Methoxy-3-nitrobenzoyloxy)-acetophenone (XIII). The acid chloride XII (69 g, 0.32 mole) was added to a solution of *o*-hydroxyacetophenone (42 ml, 0.35 mole) in 60 ml of pyridine, whereupon the mixture warmed up spontaneously. It was warmed on a water-bath (*ca.* 75°) for 15 min, cooled and then poured into 1.5 l of 4 % HCl. The light-coloured crystals were collected, washed with water and dried, affording 88 g (88 %) of almost pure XIII, m.p. 102—103°. Recrystallisation from ethanol raised the m.p. to 102.8—104°. The infrared spectrum showed bands at 1740 (ester C=O), 1685 (ketone C=O), 1530, and 1365 cm^{-1} (NO_2). (Found: C 61.60; H 4.46; N 4.55. Calc. for $C_{16}H_{13}NO_6$: C 60.95; H 4.16; N 4.44).

Baker-Venkataraman transformation of XIII: 1-(2-Hydroxyphenyl)-3-(2-methoxy-3-nitrophenyl)-propane-1,3-dione (XIV) and 2'-hydroxy-3'-nitroflavone (XV). The acetophenone derivative XIII (20.7 g, 0.065 mole) was dissolved in 60 ml of pyridine, the solution warmed to 50° and treated under stirring with 5.6 g (*ca.* 1.5 equiv.) of 85 % finely-powdered KOH. The mixture was stirred at 50—60° for 30 min by when it had assumed a dark thick consistency. The mixture was cooled, treated with 50 ml of water and the

solution filtered. It was then acidified with 50 ml of 20 % acetic acid, the orange-yellow precipitate collected, washed with water and ethanol, and dried, affording 11 g (53 %) of a bright yellow powder, which melted largely at 117°, but part of which melted above 170°. This was refluxed briefly with 150 ml of absolute ethanol, filtered and cooled, affording 7.8 g (38 %) of bright-yellow needle-like crystals, m.p. 115–117°. The infrared spectrum showed bands at 1615 (C=O), 1520, and 1370 cm^{-1} (NO_2). An analytical sample of XIV had m.p. 116.2–117.7°. (Found: C 61.62; H 4.59; N 4.45. Calc. for $C_{16}H_{13}NO_6$: C 60.95; H 4.16; N 4.44).

In one experiment carried out in essentially the same manner with 90 g (0.285 mole) of the acetophenone derivative XIII, but where a temperature of 85° was maintained for about 10–15 min, 61 g (76 %) of a light-yellow powder, m.p. 322–324°, was obtained. Recrystallisation from dimethyl sulphoxide-ethanol gave pale-yellow micro needles, m.p. 331–332°, of a compound analysing correctly for the flavone XV. The infrared spectrum showed bands at 3300–2400 (OH), 1625 (C=O), 1520, and 1380 cm^{-1} (NO_2). (Found: C 63.59; H 3.23; N 4.89. Calc. for $C_{15}H_9NO_5$: C 63.61; H 3.20; N 4.95).

2'-Methoxy-3'-nitroflavone (XVI). The diketone XIV (28 g, 0.089 mole) was suspended in 150 ml of glacial acetic acid, 4.8 ml of concentrated sulphuric acid were carefully added, and the mixture heated on a water-bath for 1.5 h with occasional shaking. The reaction mixture was cooled, poured onto crushed ice and the voluminous gelatinous precipitate collected and washed with water. Vacuum drying over a hot water-bath afforded 23.6 g (86 %) of a pale-yellow product, m.p. 99–102°. Two recrystallisations from benzene-ligroin raised the m.p. to 102–103.5°. The infrared spectrum showed bands at 1645 (C=O), 1525, and 1350 cm^{-1} (NO_2). (Found: C 65.66; H 3.85; N 4.44. Calc. for $C_{16}H_{11}NO_5$: C 64.64; H 3.73; N 4.71).

3'-Amino-2'-methoxyflavone (XVII). The flavone XVI (22.3 g, 0.075 mole) was suspended in 250 ml of 96 % ethanol, 25 ml of concentrated ammonia was added, followed by the addition of 5 g of a 5 % $Pd/CaCO_3$ catalyst. The mixture was reduced in a Parr hydrogenation apparatus at 2.1 kg/cm^2. After hydrogenation, which was completed within 30 min, the mixture was filtered to remove catalyst, solvent was removed under vacuum, and the residual product triturated with petroleum ether and collected, affording 19.6 g (98 %) of a whitish powder, m.p. 121–123°. Recrystallisation from benzene afforded pale-beige crystals m.p. 125–125.6°. The infrared spectrum showed bands at 3420, 3325 (NH_2), and 1640 cm^{-1} (C=O). (Found: C 72.09; H 4.85; N 5.30. Calc. for $C_{16}H_{13}NO_3$: C 71.90; H 4.90; N 5.24).

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