IMPROVED SYNTHESIS OF ESCULETIN

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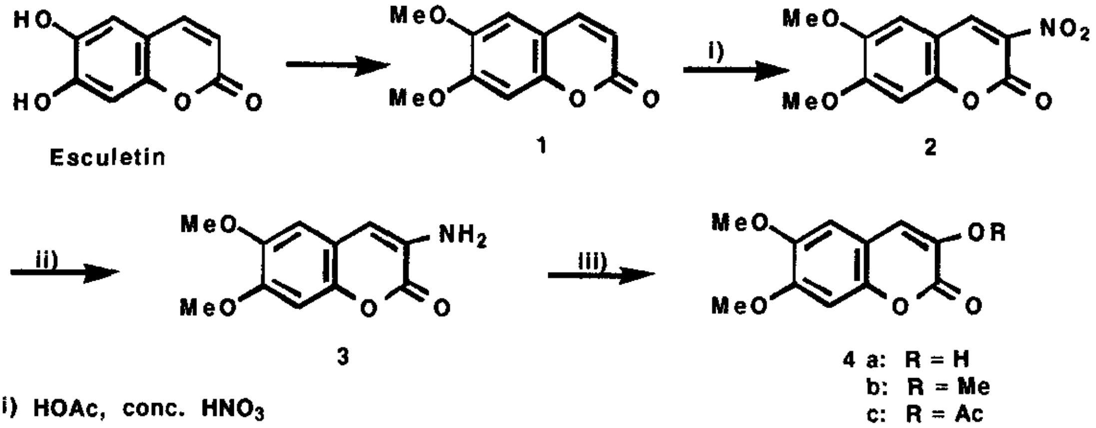
Abstract - An improved synthesis of esculetin (6,7-dihydroxycoumarin) and 3-hydroxy-6,7-dimethoxycoumarin (**4a**) is described.

In connection with another project we required 3-hydroxy-6,7-dimethoxycoumarin (**4a**). Direct hydroxylation of coumarins at the 3-position usually utilizes rat-liver microsomes, and depends on cytochrome P-450 enzymes.[1-3] More recently, a Cu^{2+}-ascorbic acid-oxygen system has been reported as effecting 3-hydroxylation of some coumarins in yields varying from 2-19%.[4]

The literature revealed two other methods of synthesis for compound (**4a**), one involving the condensation of 2-acetoxy-4,5-dimethoxybenzaldehyde with acetylglycine followed by hydrolysis of the resulting azlactone, in overall yield of 24%.[5] The other approach is as outlined in Scheme 1.[6]

Späth and Dobrovolny utilized 6,7-dimethoxycoumarin (scoparone) as a starting material, formed the 3-nitro derivative which they reduced and then hydrolysed to give **4a** in 34% yield based on **1**. The latter method seemed the more readily approachable. 6,7-Dimethoxycoumarin and its dihydroxy analogue, esculetin, are relatively expensive starting materials however, and so needed to be synthesized. The Pechmann reaction of 1,2,4-triacetoxybenzene and (±)-malic acid in sulfuric acid (97%)

for one hour at 80-100 °C is reported to produce esculetin in 30% yield.[7] Even if the methylation of esculetin to its dimethyl ether went quantitatively, the yield of the corresponding 3-hydroxycoumarin by the method of Späth *et al.* would become 10% from readily available 1,2,4-triacetoxybenzene. Our first concern was therefore to improve the yield of the Pechmann reaction.



i) HOAc, conc. HNO_3
ii) $SnCl_2$, conc. HCl, 50 °C iii) dil. HCl

Scheme 1

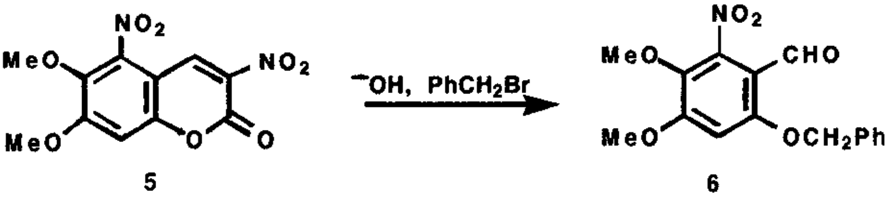
It was found that this preparation produced only a small amount of the desired product as a precipitate and even after extensive extraction with ethyl acetate, the reported yield was not achieved. After many variations of temperature and reaction times, the optimum conditions were arrived at which produced esculetin in a vastly improved yield of 85% (cf. 30%[7]). The major requirements here are:-

i) a very intimate mixture of the starting reagents, and

ii) effective and continuous stirring during the reaction.

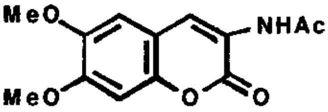
With esculetin in hand, compound (4a) was the next target. Methylation with potassium carbonate and methyl iodide in refluxing acetone gave **1** in 81% yield. (We also note the preparation of **1** by single electron transfer (SET) initiated photocyclization of 3,4-dimethoxycinnamic acid.[8])

The dimethoxycoumarin was then nitrated according to Späth's method . A 5% solution of the coumarin in glacial acetic acid was treated with one molar equivalent of nitric acid (70%) for five min on a steam bath. The product was a compound which had a melting point (243-245 ^{0}C, dec.) differing from that reported for 3-nitro-6,7-dimethoxycoumarin (256-259 ^{0}C, dec.),[6] but which analysed for $C_{11}H_9NO_6$ - indicating mononitration and 85% conversion. Proton nmr of this product was consistent with the structure (2).[9] Further confirmation of the position of nitration was obtained from the fragmentation of this nitro compound with sodium hydroxide as outlined in Scheme 2.



The reaction of sodium hydroxide with 3-nitrocoumarins which are unsubstituted at position-4, to produce aldehydes by rupture of the lactone ring, is well known.[10] When compound (2) was treated with sodium hydroxide and the product benzylated, the known 2-benzyloxy-4,5-dimethoxybenzaldehyde[11] was obtained.

The nitrocoumarin (2) was then converted to the corresponding acetamido compound (5) rather than the amino compound, because the hydrolysis of the former proceeded in superior yield, and the recovery of the acetamido compound from the reaction mixture was better, the amine being more water-soluble. (The aminocoumarin (3) is readily converted to 5 on reaction with acetic anhydride and perchloric acid.)



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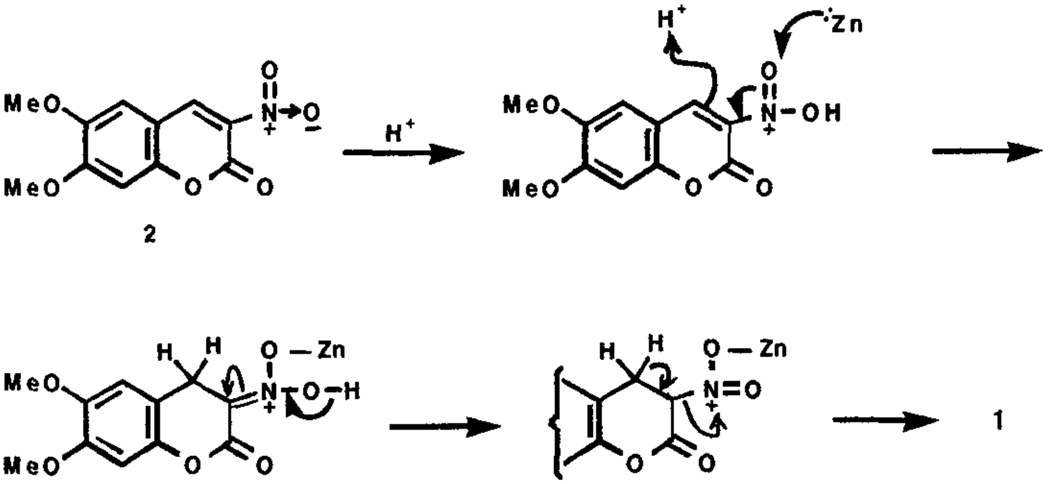
Reaction of the nitrocoumarin with zinc powder, acetic anhydride and acetic acid produced the acetamidocoumarin (5) as the major product, with the 3-aminocoumarin and 6,7-dimethoxycoumarin as minor products. Optimum conditions were found to be a 2.5% solution of **2** in acetic acid - acetic anhydride (1:1) reacting with 7.7 molar equivalents of zinc powder at room temperature for 5 h . This gave **5** in 63% yield after isolation. The amino compound was also obtained in 4% yield. When the reaction time was extended to 24 h, the overall yield fell significantly so that only 13% of **5** was obtained, with 3% of compound (3) and 7% of **1** being produced. The table below shows the distribution of products obtained under various conditions of reaction of compound (2) with zinc in acetic acid at room temperature.

Table 1. Reaction of compound (2) with Zn/HOAc/Ac_2O

Molar equivs. of zinc	2.5% Solution of (2) in solvent	Reaction time (h)	% Products (5)	(3)	(1)
7.7	glacial acetic acid	1.5	41	8	8
7.7	90% aq. acetic acid	1.5	25	28	3
7.7	glacial HOAc-Ac_2O (1:1)	5	63	4	--
7.7	glacial HOAc-Ac_2O (1:1)	24	13	3	7
20	glacial HOAc-Ac_2O (1:1)	24	18	3	8

Not only was the reaction producing amino- and acetamidocoumarin, but the compound (1) was also being formed. It seemed possible that this compound was being formed at the expense of the desired acetamide. When compound (5) in acetic anhydride-acetic acid (1:1) was treated with 8 mol of zinc for extended time however, there was no change. Reaction of zinc with the nitrocoumarin is probably occurring as shown in Scheme 3, to form compound (1).

Hydrolysis of compound (**5**) to the hydroxycoumarin (**4a**) was achieved by refluxing a 5% solution in 3M HCl, under an atmosphere of nitrogen for 4 h and removing the HCl *in vacuo*. This proceeded in 82% yield, but the melting point of the product (185-188 ^{0}C) differed from that reported for 3-hydroxy-6,7-dimethoxycoumarin (222-223 ^{0}C).[5,6] The structure of the product was however confirmed as **4a** by its positive reaction to $FeCl_3$, its nmr and ms data,[12] and by analysis of its methylation and acetylation products (**4b**) and (**4c**).



Scheme 3

Direct conversion of **1** to **5** in 60% yield without isolation of the intermediate nitrocoumarin (**2**) is also possible. Nitration of **1** is set up and after 5 min on a steam bath the mixture is diluted to 50% of its original concentration with a mixture of acetic anhydride - acetic acid (1:1) and cooled in ice. Zinc powder is then added, the mixture stirred at room temperature for 6 h. and the desired compound (**5**) isolated.

This sequence (1 ⟶ 5 ⟶ 4a) represents a 49% conversion of the coumarin (1) to 3-hydroxy-6,7-dimethoxycoumarin (*cf.* 34% by Späth *et al.*) and, due to the vastly improved synthesis of esculetin, a 31% conversion of 1,2,4-triacetoxybenzene to **4a** as compared with 10% from previously existing methods.

EXPERIMENTAL

Melting points were determined on a Kofler stage apparatus. Ultraviolet spectra were measured on a Varian Cary 219 instrument and are for ethanol solutions. Infrared spectra were obtained on a Perkin Elmer model 735B spectrophotometer and are for chloroform solutions. Proton magnetic resonance spectra were obtained in deuteriochloroform solutions on a Bruker 90 MHz spectrometer.

Esculetin: A very intimate mixture of 1,2,4-triacetoxybenzene (20.0 g, 79.4 mmol) and (±)-malic acid (11.7 g, 83.3 mmol) was made. (This was done by combining several small portions of acid and triacetoxybenzene which had been powdered in a mortar.) The mixture was then added, in one addition, to concentrated sulfuric acid (32 ml) in a large beaker and the mixture stirred at room temperature for about 5 min (Initially there was strong effervescence. Stirring at room temperature before heating ensured that the mixture did not froth over.) After this time, the mixture was heated on a steam bath (100 ^{0}C) with continuous stirring by mechanical stirrer, till all gases had evolved (about one hour). Heating and stirring were then continued for a further hour. The mixture was cooled, poured onto crushed ice (250 g) and left in the refrigerator overnight. The brown precipitate formed was collected by filtration, washed with water, and dried to provide esculetin (12.01 g, 85%), m p 274-276 ^{0}C (ethanol-water), (lit.,[5,6] 276 ^{0}C).

Conversion of esculetin to 1: Esculetin (4.0 g, 22.5 mmol), potassium carbonate (15.53 g, 112.4 mmol) and methyl iodide (5.6 ml, 90 mmol) were refluxed overnight in acetone (100 ml). The mixture was filtered and the acetone solution concentrated *in vacuo* to give pure **1** (3.77g, 81%). mp 143-144 ^{0}C (water), (lit.,[6] 144 ^{0}C).

Direct conversion of 1 to 5: Compound (**1**) (2.87 g, 13.9 mmol) was suspended in acetic acid (57 ml) and warmed to solution. Concentrated nitric acid (70%, 1.12 ml, 14.3 mmol) was added. The mixture was heated on a steam bath for 5 min with swirling, then was diluted with acetic anhydride-acetic acid (60 ml : 60 ml) and cooled in ice. Activated zinc powder (12.06 g. 0.185 mol) was added to the cooled suspension and the mixture stirred for 5 h. The mixture was then filtered to remove excess zinc, the filtrate concentrated *in vacuo* and the residue triturated with water to remove zinc acetate, leaving compound (**5**) as a pale brown solid. Extraction of the aqueous solution with chloroform yielded more **5**, (total 2.15 g, 59%). mp 224-226 ^{0}C (acetone). Uv 248, 273, 285, 308 and 351 nm; ir ν 1689 and 1713 cm^{-1}; ^{1}H-nmr δ 2.22 (3H, s, CH_3-CO), 3.92 (6H, s), 6.80 and 6.87 (each 1H, s), and 8.57 (1H, s); ms m/z 263 (M^+, 65) and 221 (100). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.40; H, 5.03; N, 5.36.

Compound (4b): Compound (**4a**) (220 mg, 1 mmol), potassium carbonate (553 mg, 4 mmol) and methyl iodide (0.36 ml, 6 mmol) were refluxed in acetone (10 ml) for 3 h. The mixture was filtered, the acetone solution concentrated *in vacuo* and the residue recrystallized from acetone/petroleum ether to give **4b** (191 mg, 82%), mp 147-149 ^{0}C (lit.,[6] 148-150 ^{0}C). Uv λ_{max} 334, 297, 286, 264, 257, and 230 nm; ir ν_{max} 1728 cm^{-1} (CO); ^{1}H-nmr δ 3.97 (3H, s), 4.00 (6H, s), and 6.87 (3H, s). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.00; H, 5.12. Found: C, 60.95; H, 4.96.

Compound (4c): To **4a** (75 mg, 0.34 mmol) in acetic anhydride (2 ml, 21.2 mmol) was added 2 drops of 62-64% $HClO_4$. The mixture was swirled until a solution was obtained (~10 min). After a further 10 min. the mixture was poured into water (20 ml) and extracted with ethyl acetate (3x10 ml). The ethyl acetate solution was dried (Na_2SO_4), concentrated *in vacuo* and the residue recrystallized from methanol to give **4c** (76 mg, 85%) as straw-coloured crystals, mp 114-115 ^{0}C. Uv λ_{max} 344, 298, and 236 nm; ir ν_{max} 1727 and 1778 cm^{-1} (CO); ^{1}H-nmr δ 2.30 (3H, s), 3.87 (6H, s), 6.77 (2H, s), and 7.32 (1H, s). Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.08; H, 4.57. Found: C, 59.39; H, 4.35.

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9. **Compound (2):** Uv λ_{max} 404, 326, 259 and 229 nm; ir ν_{max} 1743 cm^{-1} (CO); ^{1}H-nmr δ 3.83 (3H, s), 3.97 (3H, s), 7.17 (1H, s), 7.47 (1H, s) and 9.10 (1H, s).
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12. **Compound (4a):** Uv λ_{max} 343, 266, 230(sh), and 210 nm; ir ν 1712 cm^{-1} (CO); ^{1}H-nmr δ 3.88 (6H, s), 6.75 (1H, s), 6.82 (1H, s), and 6.95 (1H, s); ms m/z 222 (M$^+$, 100), 207 (29).

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