Use of Hypervalent Iodine Oxidation for the *C*(3)-Hydroxylation of Chromone, Flavone and α-Naphthoflavone

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C(3)-Hydroxylation of chromone (**1a**), flavone (**1b**) and α-naphthoflavone (**4**) *via* acid-catalysed hydrolysis of the corresponding β-methoxy-α-hydroxydimethylacetals (**2a**, **2b**, and **5**) formed by iodobenzene diacetate-potassium hydroxide methanol oxidation is described.

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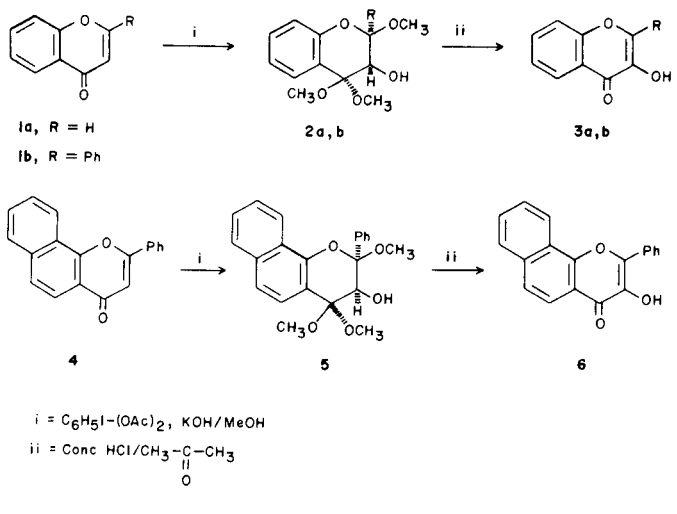
In a previous communication [1], we reported that reaction of chromone (**1a**), and flavone (**1b**) with iodobenzene diacetate and methanolic potassium hydroxide leads to α-hydroxy-β-methoxydimethylacetals **2a** and **2b**, respectively. We now report that hydrolysis of acetals **2a** and **2b** occurs with loss of 3 molecules of methanol to give 3-hydroxychromone (**3a**) and 3-hydroxyflavone (**3b**) in excellent yield.

This result is significant because **3b** and particularly **3a** are difficult to obtain otherwise [2a,b]. The hypervalent iodine oxidative procedure developed in our laboratory [3] has also been extended for the hydroxylation of α-naphthoflavone (**4**).

Reaction of **1a** and **1b** with 1.1 equivalents of iodobenzene diacetate in potassium hydroxide/methanol gives **2a** and **2b** in 53% and 67% yield, respectively. α-Naphthoflavone (**4**), under these conditions, yields **5** in 50% conversion, and without isolation the crude reaction mixture was subjected to hydrolysis to yield crystalline 3-hydroxy-α-naphthoflavone (**6**).

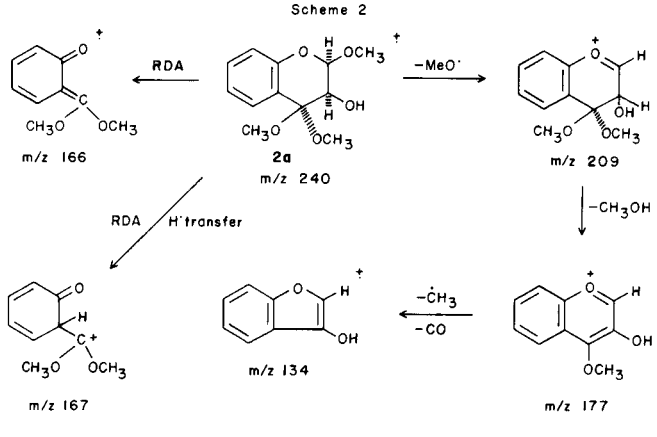
Scheme 1



The structure of **2a** and **2b** are based upon their elemental analysis and spectral data. The ^{1}H nmr of **2b** shows three singlet peaks at δ 2.95, 3.25 and 3.42 each corresponding to three protons due to the protons in the three nonequivalent $-OCH_3$ groups. The most highly shielded singlet (δ 2.95) was consisdered due to C_2-OCH_3 because *cis*-3-hydroxyflavanone dimethylacetal (**7**) [1], which does not contain C_2-OCH_3, shows only two singlets appearing at 3.20 and 3.38 due to the dimethylacetal protons. We tentatively assign C(4)α-OCH_3 as more highly shielded (at δ 3.25) because of its position below the plane of the adjacent benzene ring. These characteristic three singlet absorption peaks were also observed in case of **2a** and crude product **5**. The *cis* relationship between the C(2)-methoxyl group and the C(3)-hydroxyl group is indicated by the small value of the coupling constant (J_{2-3} = 3 Hz) [4] observed for **2a**. The other assignments are given in the Experimental section.

Mass spectral data also support the structure of intermediate dimethylacetals. The most characteristic feature in the mass spectra was well known retro-Diels Alder (RDA) fragmentation. The fragmentation pattern scheme has been outlined in Scheme 2 taking **2a** as an example. The proposed scheme of fragmentation pattern finds support

Scheme 2



from the mass spectra of related compounds reported [5a,b].

Although hydrolysis of the α-hydroxydimethyl acetal system in **2a, 2b** and **5** could proceed to give the α-hydroxy-β-methylketone, which was not observed. Loss of methanol from this presumed intermediate is a facile process due to the aromatic stabilization of the chromone system.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. The ir spectra were recorded on a Unicam SP1000 Infrared Spectrophotometer. The nmr spectra were obtained with a Varian 360 spectrometer at 60 MHz using TMS as an internal standard. Mass spectra were scanned with Hewlett Packard GC/MS 5985 apparatus at 70 eV or 20 eV.

cis-3-Hydroxy-2-methoxychromanone Dimethylacetal (**2a**).

Chromone (**1a**) (0.02 mole, 2.92 g), dissolved in 100 ml of absolute methanol, was added dropwise to a stirred solution of potassium hydroxide (0.06 mole, 3.36 g) in 50 ml of methanol over a period of 15 minutes at 5-10°. After stirring the solution for 10 minutes, iodobenzene diacetate (0.022 mole, 7.09 g) was added in 4-5 portions during 10 minutes and the resulting mixture was allowed to stir overnight. Most of the methanol was evaporated *in vacuo* and to the rsidue 100 ml of water was added. The mixture was extracted with ether (5 × 40 ml) and the combined ether extracts were dried (magnesium sulfate), filtered and evaporated *in vacuo* to yield crude **2a**, which also contains iodobenzene. Column chromatography on silica gel (100 g) using hexane:ether (50:50) as solvent system gave pure **2a**, 2.34 g (53% yield) as an oil; ir (Nujol): 3510 (-OH str) cm^{-1}; nmr (deuteriochloroform): δ 3.10 (3H s, C_2-OCH_3), 3.40 (3H, s, C_4-α-OCH_3), 3.65 (3H s, C_4-β-OCH_3), 4.06 (1H d d, C_3-*H*), 5.18 (1H d, C{-*H*) (J_{2-3} = 3 Hz), 2.5 (1H d, C}-O*H*), 6.75-7.65 (4H m, aromatic protons); ms: m/z 240 (M, 6), 209 (17), 177 (11), 167 (76), 166 (100), 134 (53), 121 (59), 105 (97), 77 (7), 75 (33).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.66. Found: C, 60.13; H, 6.72.

3-Hydroxy-2-methoxyflavanone Dimethylacetal (**2b**).

The reaction was carried out with flavone **1b** (0.02 mole) using the same conditions as described for **2a**. During work up a pale yellow solid separated when water was added to residue, obtained after removal of methanol. This solid was filtered, washed with cold water, hexane and dried on suction pump. Recrystallization from hexane yielded 4.23 g of pure **2b** (67% yield) mp 129-130°; ir (Nujol): 3500 (-O-H str) cm^{-1}; nmr (deuteriochloroform): δ 2.95 (3H, s, C_2-OCH_3), 3.25 (3H s, C_4-α-OCH_3), 3.42 (3H, s, C_3-β-OCH_3), 4.32 (1H d, C_3-*H*) (doublet collapses to singlet on addition of deuterium oxide), 6.9-7.72 (9H m, nine aromatic protons); ms: m/z 285 (M-31, 2), 253 (2), 210 (3), 167 (100), 166 (30), 165 (31), 151 (17), 134 (39), 121 (63), 120 (9), 107 (12), 105 (41), 92 (17), 91 (18), 78 (15), 77 (81).

3-Hydroxychromone (**3a**).

To a solution of **2a** (0.005 mole, 1.20 g) in acetone (10-15 ml) was added 2 ml of concentrated hydrochloric acid and the mixture was allowed to stand at room temperature for 4 hours. Colourless crystals separated out from the solution. Filtration followed by washing with cold acetone (5 ml) and drying yielded 0.72 g (90%) of pure **3a** mp 181-182° (lit [6] mp 181°).

3-Hydroxyflavone (**3b**).

Following the same procedure which was applied for **2a** — **3a, 2b** was (0.005 mole) converted into **3b** in 85% yield mp 171-172°, mmp with a commercial sample of 3-hydroxyflavone (Aldrich) remained undepressed.

3-Hydroxy-α-naphthoflavone (**6**).

α-Naphthoflavone (**4**) (0.01 mole) was reacted with iodobenzene diacetate (0.011 mole) in methanolic potassium hydroxide at room temperature according to the procedure as described for **2a**. The crude dimethylacetal [nmr (deuteriochloroform): δ 2.92 s, 3.25 s, 3.38 s] containing iodobenzene and starting material was dissolved in acetone (20 ml), filtered and to the filtrate was added 2 ml of concentrated hydrochloric acid. The resulting mixutre was allowed to stand at room temperature for 4 hours. During this time yellow crystalline **5** separated out, mp 214-215° (lit [7] mp 213-214°) yield 40%; ms: m/z 289 (M + 1, 21), 288 (M, 100), 260 (13), 232 (4), 231 (11), 170 (10), 105 (4).

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