Synthesis of Some Naturally Occurring Acetylchromenes

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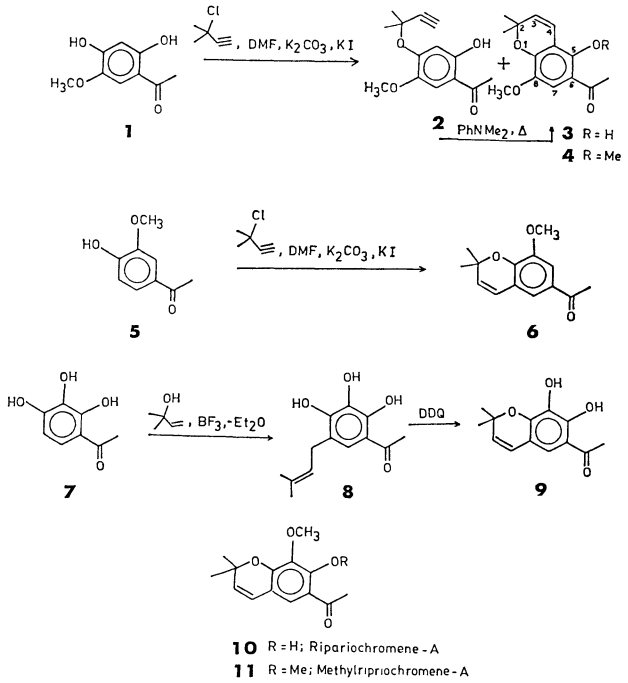
2,4-Dihydroxy-5-methoxyacetophenone on treatment with 3-chloro-3-methyl-1-butyne in the presence of K_2CO_3, KI, and DMF yielded its 4-(1,1-dimethyl-2-propynyl) ether (**2**) and the naturally occurring 6-acetyl-5-hydroxy-8-methoxy-2,2-dimethylchromene (**3**). More of the chromene (**3**) could be obtained by the thermal cyclisation of the acetophenone (**2**). Methylation of **3** yielded another natural chromene. 4-Hydroxy-3-methoxyacetophenone, on similar treatment with 3-chloro-3-methyl-1-butyne, gave directly natural 6-acetyl-8-methoxy-2,2-dimethylchromene. 2,3,4-Trihydroxy-5-(3-methyl-2-butenyl)acetophenone, on cyclodehydrogenation followed by methylation with 1 mol of dimethyl sulfate, yielded natural ripariochromene-A. Further methylation provided methylripariochromene-A.

From a Mexican plant *Ageratina scorodonioides* (Gray) King et Rob., Bohlmann *et al.*[1] isolated 6-acetyl-5-hydroxy-8-methoxy-2,2-dimethylchromene (**3**) and its methyl ether (**4**). The former was also reported to occur in *Flourensia cernua* D.C.[2] Obviously, both seem to be derived in nature from 2,4-dihydroxy-5-methoxyacetophenone (**1**). They are now synthesised from this ketone **1** by heating with 3-chloro-3-methyl-1-butyne in the presence of K_2CO_3, KI, and DMF, when a mixture of two compounds resulted. The major compound proved to be the required natural chromene **3** on the basis of its NMR spectrum and positive ferric chloride reaction. Thus, it showed a characteristic doublet of two olefinic protons at δ 5.50 and 6.70 and a singlet of only one aromatic proton at δ 7.05. Further it was found to be identical in all respects with the description of the natural sample. The minor component was characterised as 2-hydroxy-5-methoxy-4-(1,1-dimethyl-2-propynyloxy)acetophenone (**2**) on the basis of resonance signals of one acetylenic proton at δ 2.70 and of two *para*-coupled aromatic protons at δ 6.88 and 7.20. The yield of the natural chromene **3** was raised by heating **2** with *N,N*-dimethylaniline. When the chromene (**3**) was methylated with excess of dimethyl sulfate in the presence of ignited K_2CO_3 and acetone, the fully methylated chromene **4** identical with the natural sample was obtained.

From *A. scorodonioides*, Bohlmann *et al.*[1] isolated still another chromene to which they gave the constitution of 2,2-dimethyl-6-acetyl-8-methoxychromene (**6**) on the basis of its NMR spectrum. It is now prepared from 4-hydroxy-3-methoxyacetophenone (**5**) by heating it with 3-chloro-3-methyl-1-butyne in the presence of DMF, K_2CO_3, and KI, when the natural chromene (**6**) was straight away obtained identical in all respects with the description of the natural substance.

From *Eupatorium riparium* Regel., Anthonsen[3] isolated two chromenes called ripariochromene-A and methylripariochromene-A. They were assigned structures as 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethylchromene (**10**) and its methyl ether (**11**) respectively mainly on the basis of their NMR data. More recently, these two compounds have also been isolated from the above mentioned species of *Ageratina*.[1] Methylripariochromene-A **11** has also been obtained from the dried leaves of *Stevia serrata* by Kohda *et al.*[4] who



concluded this structure from a study of nuclear Overhauser effect in its PMR spectrum and its ^{13}C NMR spectrum.

These two compounds **10** and **11** have now been synthesised starting from 2,3,4-trihydroxyacetophenone **1** which, on reacting with 2-methyl-3-buten-2-ol in the presence of BF_3-etherate according to the procedure of Bajwa *et al.*,[5] gave 2,3,4-trihydroxy-5-(3-methyl-2-butenylacetophenone (**8**) as the main product. Cyclodehydrogenation of **8** with DDQ afforded 6-acetyl-7,8-dihydroxy-2,2-dimethylchromene (**9**) in nearly quantitative yield. Its structure was established on the basis of its NMR spectrum which showed 2 doublets at δ 5.53 and 6.20 and an aromatic proton at δ 7.25. Partial methylation of **9** with dimethyl sulfate, K_2CO_3 and acetone yielded ripariochromene-A **10**, while complete methylation with excess of dimethyl sulfate afforded methylripariochromene-A **11** both identical with the natural samples.

Experimental

All melting points are uncorrected. Unless otherwise stated, PMR spectra were determined on a BS 487 C spectrometer (80 MHz) with reference to tetramethylsilane as an

internal standard; the chemical shifts are expressed in δ values; light petroleum used had boiling range 60—80 °C; silica gel was used for column chromatography and silica gel-G for TLC; R_f values refer to TLC using one of the following solvent systems: (A) toluene–ethyl formate–formic acid (5:4:1); (B) benzene; (C) benzene–ethyl acetate (9:1); spraying of TLC plates was carried out with 10% aq H_2SO_4 and/or 1% alcoholic $FeCl_3$.

*Reaction of 2,4-Dihydroxy-5-methoxyacetophenone (**1**) with 3-Chloro-3-methyl-1-butyne.* A mixture of the ketone[6] (**1**, 0.5 g) 3-chloro-3-methyl-1-butyne (0.4 ml), ignited potassium carbonate (2.5 g), anhydrous potassium iodide (1 g) and *N,N*-dimethylformamide (40 ml) was heated at 80—85 °C for 40 h. The solvent was removed *in vacuo*, the residue treated with water (200 ml) and the whole mixture extracted with ether. The ether residue on column chromatography and successive elution with benzene–light petroleum (1:1) and benzene alone gave two fractions A and B.

Fraction-A crystallized from benzene-light petroleum mixture to afford *6-acetyl-5-hydroxy-8-methoxy-2,2-dimethylchromene* (**3**, 200 mg) as yellow needles, mp 87—88 °C (lit,[2] mp 88 °C); R_f 0.45 (solvent B), brown ferric reaction; PMR ($CDCl_3$): 1.48 (6H, s, $(CH_3)_2C<$), 2.46 (3H, s, $-COCH_3$), 3.74 (3H, s, $-OCH_3$), 5.50 (1H, d, J=10 Hz, H-3), 6.70 (1H, d, J=10 Hz, H-4), 7.05 (1H, s, H-7) and 12.55 (1H s, chelated OH); UV_{max} (MeOH): 255 nm (log ε 4.31), 320 (3.31), 3.40 (3.74). (Found: C, 68.0; H, 6.2%). These data agree with those of the natural substance.

Fraction-B gave *2-hydroxy-5-methoxy-4-(1,1-dimethyl-2-propenyloxy)acetophenone* (**2**) as a yellow oil (100 mg); R_f 0.4 (solvent B); green ferric reaction; PMR (CCl_4): 1.25; 1.41 (6H, 2s, $(CH_3)_2C<$), 2.50 (3H, s, $-COCH_3$), 2.70 (1H, s, $-C\equiv\underline{C}H$), 3.80 (3H, s, $O\underline{C}H_3$), 6.88 (1H, d, J=1.5 Hz, H-3) and 7.20 (1H, d, J=1.5 Hz, H-6); UV_{max} (MeOH): 281 nm (log ε 4.2), 302 (3.9). Found: C, 68.2; H, 6.8. Calcd for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5%.

*6-Acetyl-5-hydroxy-8-methoxy-2,2-dimethylchromene (**3**).* The above acetophenone (**2**) (50 mg) was heated in *N,N*-dimethylaniline at 210—220 °C for 3 h. The mixture was cooled and treated with dil HCl (1:1, 20 ml). The resulting solid crystallized from benzene-light petroleum mixture to give **3** as yellow needles (40 mg), identical in mp and mmp with the sample prepared above.

*6-Acetyl-5,8-dimethoxy-2,2-dimethylchromene (**4**).* A solution of **3** (100 mg) in acetone (20 ml) was refluxed with dimethyl sulfate (0.06 ml) and ignited K_2CO_3 (400 mg) for 4 h. Acetone was evaporated and water added to the residue. The resulting solid crystallised from ether–light petroleum mixture to give **4** as yellow crystals, mp 62—63 °C (lit,[1] mp 63 °C); R_f 0.55 (solvent B); PMR (CCl_4): 1.48 (6H, s, $(CH_3)_2C<$), 2.50 (3H, s, $-COC\underline{H}_3$), 3.77 (6H, s, two $-OC\underline{H}_3$), 5.53 (1H, d, J=10 Hz, H-3) 6.48 (1H, d, J=10 Hz, H-4) and 7.22 (1H, s, H-7); UV_{max} (MeOH): 270 nm (log ε 3.2), 281 (3.1), 310 (3.9). (Found: C, 68.8; H, 7.21%). These data agree with those described for the natural sample.

*6-Acetyl-8-methoxy-2,2-dimethylychromene (**6**).* A mixture of 4-hydroxy-3-methoxyacetophenone[7] (**5**, 500 mg), 3-chloro-3-methyl-1-butyne (0.2 ml), K_2CO_3(2 g), KI (1 g), and DMF (20 ml) was heated on a steam bath for 45 h. The product gave **6** as a colourless oil (300 mg), R_f 0.6 (solvent C); PMR ($CDCl_3$): 1.48 (6H, s, $(CH_3)_2C<$), 2.57 (3H, s, $-COCH_3$), 3.90 (3H, s, $-OCH_3$), 5.55 (1H, d, J=10 Hz, H-3), 6.30 (1H, d, J=10 Hz, H-4) 7.25 (1H, d, J=2 Hz, H-7), and 7.50 (1H, d, J=2 Hz, H-5); UV_{max} (MeOH): 225 nm (log ε 3.31), 302 (3.90). These data are in accord with those of the natural substance.[1]

*6-Acetyl-7,8-dihydroxy-2,2-dimethylchromene (**9**).* To a solution of 2,3,4-trihydroxy-5-(3-methyl-2-butenyl) acetophenone[5] (**8**, 1 g) in dry benzene (50 ml) was added DDQ (1 g) and the resulting mixture refluxed for 15 min, when colorless hydroquinone separated out. It was filtered while hot and the filtrate after removal of the solvent left a viscous mass which was purified by column chromatography. Elution with benzene–light petroleum (1:1) gave **9** as a dense yellow oil (850 mg); R_f 0.83 (solvent A); dark brown ferric reaction; PMR ($CDCl_3$): 1.47 (6H, s, $(CH_3)_2C<$), 2.50 (3H, s, $-COCH_3$), 5.53 (1H, d, J=10 Hz, H-3), 6.20 (1H, d, J=10 Hz, H-4), 7.25 (1H, s, H-5) and 12.30 (1H, s, chelated OH); UV_{max} (MeOH); 230 nm(log ε 4.2), 246 (3.9) and 270 (3.1).

*Ripariochromene-A (**10**).* A solution of the above chromene (**9**, 130 mg) in dry acetone (20 ml) was refluxed with dimethyl sulfate (0.06 ml) and ignited K_2CO_3 for 3 h. The product crystallised from ethyl acetate–light petroleum mixture to give **10** as yellow crystals (100 mg), mp 88—89 °C (lit,[1] mp 88.5 °C); R_f 0.65 (solvent C); brown ferric chloride reaction; PMR ($CDCl_3$): 1.45 (6H, s, $(CH_3)_2C<$), 2.58 (3H, s, $COCH_3$), 3.83 (3H, s, $OC\underline{H}_3$), 5.55 (1H, d, J=10 Hz, H-3), 6.30 (1H, d, J=10 Hz, H-4), and 7.20 (1H, s, H-5); UV_{max} (MeOH); 242 nm (log ε 3.2), 292 (3.1). (Found: C, 68.0; H, 6.2%). These data agree with those described for the natural compound.[1]

*Methylripariochromene-A (**11**).* An acetone solution of the chromene (**9**, 130 mg) was refluxed with dimethyl sulfate (0.15 ml) and ignited K_2CO_3 for 5 h. The product (**11**) was obtained as a light yellow oil (100 mg), R_f 0.75 (solvent A); PMR ($CDCl_3$): 1.45 (6H, s, $(CH_3)_2C<$), 2.48 (3H, s, $-COCH_3$), 3.75 (6H, s, two $-OC\underline{H}_3$), 5.55 (1H, d, J=10 Hz, H-3), 6.24 (1H, d, J=10 Hz, H-4) and 7.27 ppm (1H, s, H-5); UV_{max} (MeOH): 255 nm (log ε 3.6), 286 (3.2). (Found: C, 68.8; H, 7.4%). It agreed with the natural substance.[1]

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