Chromone Studies. Part 13.[1] Synthesis and Electron-Impact Mass Spectrometric Studies of 5-Hydroxy-2-isopropyl-7-methoxychromone, a Constituent of the Medicinal Plant *Baeckea frutescens,* and Side-Chain Analogues

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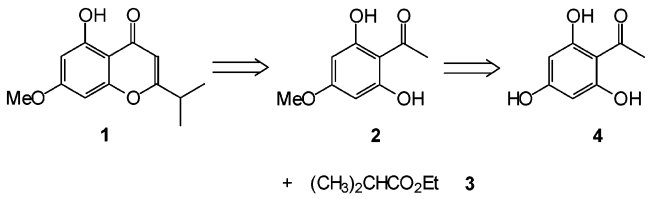
5-Hydroxy-2-isopropyl-7-methoxychromone (**1d**), a chromone constituent isolated from the aerial parts of *Baeckea frutescens*, and four analogues (**1a**−**c** and **1e**), all of which exhibit toxicity to the brine shrimp *Artemia salina*, have been prepared from 2′,4′,6′-trihydroxyacetophenone. High-resolution mass spectrometric analysis has permitted elucidation of the fragmentation patterns exhibited by these systems following electron-impact ionization.

Chromones are widely distributed in nature, and many are known to possess useful medicinal properties.[2] Among these are the chromone derivatives, granulosin [7,8-(methylenedioxy)-2-propylchromone], isolated by Schiff and coworkers[3] from the bark of *Galipea granulosa*, and 5-hydroxy-2-isopropyl-7-methoxychromone **1d**, recently isolated by Tsui and Brown[4] from the aerial parts of *Baeckea frutescens* L., a plant used in traditional Chinese medicine for treating rheumatism and snake-bite. As part of an ongoing study of chromone systems, we previously described an efficient synthesis of granulosin and structural analogues[5] and now report the preparation of 5-hydroxy-2-isopropyl-7-methoxychromone (**1d**) and several analogues (**1a**−**c** and **1e**), their toxicity to the brine shrimp *Artemia salina*, and an investigation of their EIMS fragmentation patterns.

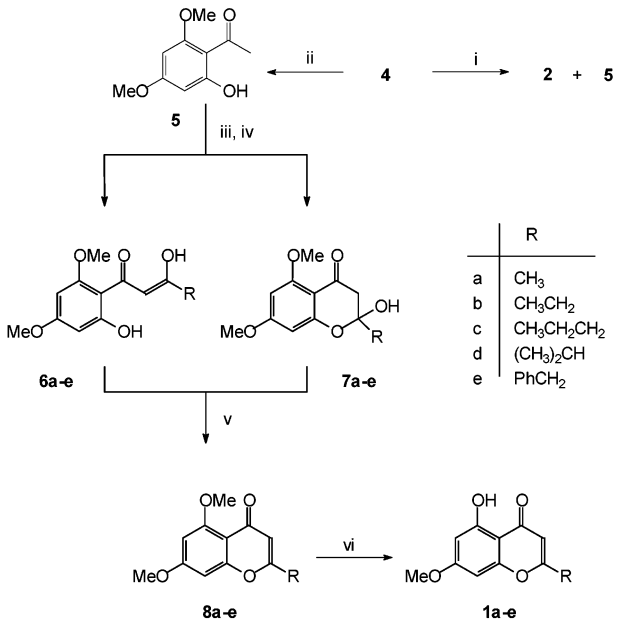
Retrosynthetic analysis suggested that synthesis of **1d** could be achieved via the condensation of ethyl 2-methylpropanoate (**3**) with 2′,6′-dihydroxy-4′-methoxyacetophenone (**2**), obtainable, in turn, from 2′,4′,6′-trihydroxyacetophenone (**4**) (Scheme 1). However, attempted methylation of the commercially available **4**, using 1 equiv of dimethyl sulfate and 1 equiv of K_2CO_3, as described by Huang et al.,[6] gave a mixture, shown by ^{1}H NMR analysis to comprise the desired 2′,6′-dihydroxy-4′-methoxyacetophenone (**2**; <40%), the dimethylated analogue (**5**), and starting material. Consequently, it was decided to exploit the facile dimethylation and attempt selective demethylation of the 6′-methoxy group later in the synthetic sequence. The resistance of the 2′-hydroxy group to methylation under these conditions is attributed to hydrogen-bonded chelation with the acetyl carbonyl oxygen. The existence of such hydrogen bonding is clearly evident in the significant deshielding of the 2-hydroxyl proton (δ_H ca. 13.9) in the ^{1}H NMR spectrum of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**5**). Following this strategy (Scheme 2), reaction of **4** with 2 equiv of dimethyl sulfate and 2 equiv of anhydrous K_2CO_3 in acetone under reflux for 5 h gave **5**[7] in 90% yield. The ^{13}C NMR spectrum of **5** revealed nine distinct carbon signals, instead of the expected 10, the intense signal at δ_C 55.4 reflecting coincidence of the two methoxy carbon signals, a conclusion supported by COSY, HMQC, and HMBC data.

The dimethylated intermediate (**5**) was then treated with 2 equiv of NaOEt in EtOH to afford an enolate which, on reaction with the series of ethyl carboxylate esters [RCO_2Et; R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $(CH_3)_2CH$, $PhCH_2$], gave mixtures, indicated by ^{1}H NMR spectroscopy, to contain the corresponding *C*-acylated products (existing as the respective enol tautomers, formulated as structures **6a**−**e**) and their cyclized derivatives **7a**−**e**. Treatment of these mixtures with HOAc and H_2SO_4 afforded the 5,7-dimethoxychromone derivatives **8a**−**e**. Selective demethylation at the C-5 position was achieved in yields ranging from 55 to 80%, using a mixture of boiling Ac_2O and hydriodic acid,[8] and the structures of the resulting 5-hy-

Scheme 1



Scheme 2[a]



[a] Reagents: (i) Me_2SO_4 (1 equiv), K_2CO_3 (1 equiv), acetone; (ii) Me_2SO_4 (2 equiv), K_2CO_3 (2 equiv), acetone; (iii) NaOEt, EtOH; (iv) RCO_2Et; (v) AcOH, H_2SO_4; (vi) Ac_2O, HI, 115 °C, 30 min.

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Table 1. Summary of *Artemia salina* Biological Assay Data for Compounds **1a**−**e**[a]

		95% confidence interval (μg.mL^{-1})	
compd	LC_{50} (μg mL^{-1})	upper limit	lower limit
1a	112.2	94.8	132.9
1b	39.0	35.7	42.6
1c	31.5	27.4	36.4
1d	23.8	21.2	26.8
1e	516.6	445.4	599.2

[a] Estimates of median lethal concentrations obtained using the trimmed Spearman−Karber method.[9]

Table 2. Summary of *Artemia salina* Biological Assay Data for Compounds **8a**−**e**[a]

		95% confidence interval (μg.mL^{-1})	
compd	LC_{50} (μg mL^{-1})	upper limit	lower limit
8a	315.1	223.9	443.3
8b	200.1	182.3	219.7
8c	106.0	95.0	118.3
8d	94.2	82.5	107.5
8e	247.3	217.1	281.8

[a] Estimates of median lethal concentrations obtained using the trimmed Spearman−Karber method.[9]

droxy-7-methoxychromone derivatives (**1a**−**e**) were confirmed by HREIMS and spectroscopic (IR, ^{1}H and ^{13}C NMR) analysis. The spectroscopic data obtained for 5-hydroxy-2-isopropyl-7-methoxychromone (**1d**) corresponded to those reported for the natural product.[4]

To evaluate the biological activity of the 2-alkyl-5-hydroxy-7-methoxychromones (**1a**−**e**) and their 5,7-dimethoxy precursors (**8a**−**e**), *Artemia salina* larvicidal bioassays were performed using the method reported by Solis et al.[9] The trimmed Spearman−Karber method[10] was used to obtain estimates of median lethal concentrations of the *A. salina* mortality data for compounds **1a**−**e** and **8a**−**e**. The LC_{50} values obtained for the monomethoxy analogues **1a**−**e** (Table 1) indicate that they are, in general, considerably more active than the dimethoxychromone derivatives **8a**−**e** (Table 2). These data are consistent with the observation by Nohara and co-workers[11] that the presence of hydroxyl groups on the homocyclic ring is important for biological activity in chromone systems. While compounds **1a**−**d** all exhibit significant cytotoxicity (LC_{50}: 23−112 ppm), the 2-benzyl derivative **1e** (LC_{50}: 517 ppm) appears to be even less active than the dimethoxy derivatives (LC_{50}: 94−315 ppm). Interestingly, of all the compounds examined, 5-hydroxy-2-isopropyl-7-methoxychromone (**1d**) proved to be most toxic against *A. salina*.

The EIMS fragmentation patterns of the monomethoxychromones **1a**−**e** and their dimethoxy analogues **8a**−**e** were investigated using a combination of low-resolution, high-resolution, and *B*/*E* linked-scan data. The fragmentation patterns proposed for 5-hydroxy-2-isopropyl-7-methoxychromone **1d** are outlined in Scheme 3 (Supporting Information) and are, largely, representative of the series **1a**−**e**. The base peak at *m*/*z* 234 corresponds to the molecular ion **Id**, which appears to fragment via five major pathways (A, B, C, D, and E). In path A, loss of a hydrogen atom leads to the resonance-stabilized, tertiary carbocation **IId** (*m*/*z* 233), decarbonylation of which affords the ring-contracted benzofuran carbocation **IVd** (*m*/*z* 205). Such ring contractions are typical of chromone derivatives.[12] In path B, loss of a methyl radical from the molecular ion gives the resonance-stabilized, secondary carbocation fragment **IIId** (*m*/*z* 219), which, like fragment **IId**, undergoes decarbonylation to give the analogous, ring-contracted fragment **VId** (*m*/*z* 191). In path C, elimination of HCHO, characteristic of aromatic methyl ethers,[13] affords the radical-cation **Vd** (*m*/*z* 204), subsequent decarbonylation of which leads to yet another ring-contracted fragment, **VIId** (*m*/*z* 176). In path D, the molecular ion **Id** undergoes the expected retro-Diels−Alder reaction (RDA), characteristic of the chromone nucleus,[12] and elimination 2-methyl-1-butyne, affording the ketene **IXd** (*m*/*z* 166); successive decarbonylation then gives the cyclopentadienyl fragments **Xd** (*m*/*z* 138) and **XId** (*m*/*z* 110). The formation of fragment **VIIId** (*m*/*z* 167) (path E) from the molecular ion is attributed to the $[RDA+H]^+$ process, which is also common in chromone derivatives;[12] subsequent deprotonation provides an alternative route to fragment **IXd**.

While most of the fragments of types **I**−**XI** were observed in the mass spectra of the analogues **1a**−**c**,**e**, additional fragments, which are supported by the linked-scan data and which arise from the presence of the phenyl group, were observed for the 2-benzyl derivative **1e** (Scheme 4, Supporting Information). Thus, formation of fragment **XIIe** (*m*/*z* 115) is attributed to heterolytic fission of the molecular ion via an RDA-type process; in this case, however, effective stabilization presumably accounts for the formation of the benzylic-propargylic carbocation. The tropylium cation **XIIIe** (*m*/*z* 91) and the phenyl cation **XIVe** (*m*/*z* 77) are typical of alkyl benzenes. Not surprisingly, the fragmentations exhibited by 2-isopropyl-5,7-dimethoxychromone (**8d**) and its side-chain analogues (**8a**−**c** and **8e**) correlate closely with those of the monomethoxy compounds **1a**−**e**.[14]

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 MHz NMR spectrometer and are referenced using the solvent signals. Low-resolution mass spectra were recorded on a Finnigan-Mat GCQ mass spectrometer, and high-resolution spectra were obtained on a VG70-SEQ double-focusing magnetic sector instrument by Dr. P. Boshoff at the Mass Spectrometry Unit, Cape Technikon, Cape Town. The experimental procedures are illustrated by the following examples.

Preparation of 5-Hydroxy-2-isopropyl-7-methoxychromone (1d). A solution of 2-isopropyl-5,7-dimethoxychromone (**8d**; 50 mg, 0.20 mmol), Ac_2O (1.01 mL, 10.7 mmol), and HI (d 1.7; 1.52 mL, 20.2 mmol) was heated at 115 °C for 30 min. The reaction mixture was cooled and then diluted with aqueous $NaHSO_3$. The resulting solution was neutralized with $NaHCO_3$, and the precipitated solid filtered off and washed with H_2O. Flash chromatography on silica gel [elution with hexane−EtOAc (5:1)] afforded **1d** as a pale yellow solid (26 mg, 55%): mp 44−46 °C (lit.,[4] 40−43 °C); IR, ^{1}H and ^{13}C NMR, EIMS, and HREIMS data were consistent with literature values.[4]

Preparation of 2′-Hydroxy-4′,6′-dimethoxyacetophenone (5).[7] A stirred solution of 2′,4′,6′-trihydroxyacetophenone (**4**; 5.0 g, 30 mmol), Me_2SO_4 (5.3 mL, 56 mmol), and anhydrous K_2CO_3 (8.2 g, 56 mmol) in acetone (90 mL) was boiled under reflux for 5 h. The reaction mixture was filtered and evaporated in vacuo. Recrystallization of the solid residue from petroleum ether (bp 80−100 °C)−hexane (1:9) afforded **5** as a pale yellow solid (5.2 g, 90%): mp 75−77 °C (lit.,[15] 77−79 °C). IR, ^{1}H and ^{13}C NMR, EIMS, and HREIMS data were consistent with literature values.[15]

Preparation of 2-Isopropyl-5,7-dimethoxychromone (8d). A mixture of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**5**; 1.0 g, 5.1 mmol) and ethyl isobutyrate (3.0 mL, 22 mmol) was added dropwise to a stirred dispersion of NaOEt [generated in situ by adding Na metal (0.51 g, 22 mmol) to dry EtOH (4.0 mL)]. The resulting mixture was boiled gently under reflux

for 8 h, during which time, a thick yellow slurry was formed. After cooling, the reaction mixture was poured into Et_2O (30 mL) and, after standing for 2 h, the sodium salt was filtered off, washed with Et_2O, and dissolved in ice-cold H_2O (15 mL). The resulting solution was acidified with HOAc and then extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to afford a brick-red residue indicated, by ^1H NMR spectroscopy, to contain a mixture of 1-(2-hydroxy-4,6-dimethoxyphenyl)-4-methyl-1,3-pentanedione (as an enol tautomer, formulated as **6d**) and 2-hydroxy-2-isopropyl-5,7-dimethoxychromanone (**7d**), which was used without further purification. The crude mixture, together with glacial HOAc (5.0 mL) and concentrated H_2SO_4 (0.1 mL), was boiled under reflux for 4 h. The hot solution was poured into ice-cold H_2O (20 mL), and the resulting mixture was basified with 10% aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to give a light brown solid. Flash chromatography on silica gel (elution with EtOAc) afforded **8d** as a white solid (0.50 g, 40%): mp 54−56 °C; IR (KBr) ν_{max} 1656 (CO) cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 1.26 (6H, d, J = 6.9 Hz, 2 × CH_3), 2.74 (1H, q, J = 6.8 Hz, CH), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.00 (1H, s, H-3), 6.32 (1H, d, J = 2.2 Hz, H-6) and 6.42 (1H, d, J = 2.2 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9 (q, 2 × CH_3), 32.5 (d, CH), 55.6 (q, OCH_3), 56.3 (q, OCH_3), 92.6 (d, C-8), 95.9 (d, C-6), 108.9 (d, C-3), 109.0 (s, C-4a), 160.2 (s, C-8a), 160.9 (s, C-5), 163.8 (s, C-7), 171.0 (s, C-2), and 177.9 (s, C═O); EIMS m/z 248 [M^+] (100); HREIMS m/z 248.1049 (calcd for $C_{14}H_{16}O_4$, 248.1049).

Compounds **1a**,[8] **8a**,[8] **8b**,[16] and **8c**[17] have been reported previously. Analytical data for other, new compounds prepared in this study are as follows.

2-Ethyl-5-hydroxy-7-methoxychromone (1b): brown solid [from hexane−EtOAc (8:2), 150 mg, 80%]; mp 101−103 °C; IR (KBr) ν_{max} 2975 (br, OH), 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (3H, t, J = 7.2 Hz, CH_3), 2.61 (2H, q, J = 7.4 Hz, CH_3CH_2), 3.87 (3H, s, OCH_3), 6.02 (1H, s, H-3), 6.32 (1H, d, J = 2.2 Hz, H-6), 6.35 (1H, d, J = 2.1 Hz, H-8), 12.67 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.9 (q, CH_3), 27.4 (t, CH_3CH_2), 55.7 (q, OCH_3), 92.4 (d, C-8), 97.9 (d, C-6), 105.4 (s, C-4a), 107.2 (d, C-3), 158.1 (s, C-8a), 162.2 (s, C-5), 165.4 (s, C-7), 171.5 (s, C-2), 182.7 (s, C═O); EIMS m/z 220 [M^+] (100); HREIMS m/z 220.0727 (calcd for $C_{12}H_{12}O_4$, 220.0736).

5-Hydroxy-7-methoxy-2-propylchromone (1c): pale yellow crystalline solid (after chromatography, 125 mg, 66%); mp 89−91 °C; IR (KBr) ν_{max} 2967 (br, OH), 1654 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (3H, t, J = 7.4 Hz, CH_3), 1.75 (2H, m, CH_3CH_2), 2.55 (2H, t, J = 7.5 Hz, $CH_3CH_2CH_2$), 3.84 (3H, s, OCH_3), 6.02 (1H, s, H-3), 6.32 (1H, d, J = 2.1 Hz, H-6), 6.35 (1H, d, J = 2.1 Hz, H-8), 12.69 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5 (q, CH_3), 20.2 (t, CH_3CH_2), 36.1 (t, $CH_3CH_3CH_2$), 55.7 (q, OCH_3), 92.5 (d, C-8), 97.9 (d, C-6), 105.5 (s, C-4a), 108.1 (d, C-3), 158.2 (s, C-8a), 162.2 (s, C-5), 165.4 (s, C-7), 170.3 (s, C-2), 182.6 (s, C═O); EIMS m/z 234 [M^+] (100); HREIMS m/z 234.0894 (calcd for $C_{13}H_{14}O_4$, 234.0892).

2-Benzyl-5-hydroxy-7-methoxychromone (1e): white crystalline solid (from EtOH, 115 mg, 61%); mp 152−153 °C; IR (KBr) ν_{max} 3000 (br, OH), 1677 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 3.83 (3H, s, OCH_3), 3.87 (2H, s, CH_2Ph), 5.96 (1H, s, H-3), 6.32 (1H, d, J = 2.1 Hz, H-6), 6.34 (1H, d, J = 2.1 Hz, H-8), 7.26−7.37 (5H, m, Ar−H) and 12.64 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.5 (t, CH_2Ph), 55.7 (q, OCH_3), 92.5 (d, C-8), 98.0 (d, C-6), 105.3 (s, C-4a), 108.9 (d, C-3), 127.5 (d, Ar−C), 128.9 (d, 2 x Ar−C), 129.2 (d, 2 × Ar−C), 134.5 (s, Ar−C), 158.1 (s, C-8a), 162.1 (s, C-5), 165.4 (s, C-7), 168.8 (s, C-2), and 182.5 (s, C═O); EIMS m/z 282 [M^+] (100); HREIMS m/z 282.0888 (calcd for $C_{17}H_{14}O_4$, 282.0892).

2-Benzyl-5,7-dimethoxychromone (8e): brown crystalline solid (after chromatography, 0.90 g, 60%); mp 170−171 °C; IR (KBr) ν_{max} 1664 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.80 (2H, s, CH_2Ph), 3.83 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.96 (1H, s, H-3), 6.30 (1H, d, J = 2.0 Hz, H-6), 6.37 (1H, d, J = 2.1 Hz, H-8), 7.25−7.34 (5H, m, Ar−H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.9 (t, CH_2Ph), 55.6 (q, OCH_3), 56.3 (OCH_3), 92.7 (d, C-8), 96.0 (d, C-6), 109.0 (s, C-4a), 112.1 (d, C-3), 127.3 (d, Ar−C), 128.8 (d, 2 × Ar−C), 129.1 (d, 2 × Ar−C), 135.0 (s, Ar−C), 160.1 (s, C-8a), 160.9 (s, C-5), 163.8 (s, C-7), 164.8 (s, C-2), and 177.4 (s, C═O); EIMS m/z 296 [M^+] (100); HREIMS m/z 296.1050 (calcd for $C_{18}H_{16}O_4$, 296.1049).

Assessment of Biological Activity. *A. salina* larvicidal bioassays were performed following the method described by Solis et al.[9] The 10% trimmed Spearman−Karber method[10] was used to obtain estimates of median lethal concentrations of *A. salina* mortality data from 12 solutions across concentration ranges of 200.0−10.0 μg mL^{-1} for compounds **1a**−**d**; 700.0−300.0 μg mL^{-1} for compound **1e**, and 400.0−50.0 μg mL^{-1} for compounds **8a**−**e**.

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Supporting Information Available: Major EIMS fragmentation pathways of **1d** (Scheme 3) and **1e** (Scheme 4). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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