

## Synthetic studies in aromatic hemiterpenes of natural origin, Part 5\* : Synthesis of 6-acetyl-2,2-dimethyl-8-methoxychromene via benzylic oxidation route

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**Abstract.** The synthesis of 6-acetyl-2,2-dimethyl-8-methoxychromene (1c), a naturally occurring isomer of enecalinalin (1a) has been described starting from 2,2,6-trimethyl-8-methoxychromene (2e) which was obtained from creosol (4) in two steps involving condensation of the phenol with malic acid to the coumarin (3), followed by Grignard reaction with  $\text{CH}_3\text{MgI}$ . The transformation of (2e) to the natural product (1c) was effected by oxidative dehydrogenation by DDQ of the 6-methyl function to the formyl group (2f), Grignard reaction to the carbinol (2g) and finally its oxidation to the acetyl moiety (1c), the sequence of the essential steps schematically summarised as :  $\text{Ar-CH}_3 \rightarrow \text{Ar-CHO} \rightarrow \text{Ar-CH(OH)CH}_3 \rightarrow \text{Ar-COCH}_3$ .

**Keywords.** Aromatic hemiterpenes; coumarins; chromenes; benzylic oxidative dehydrogenation by DDQ.

### 1. Introduction

We have recently developed two convenient routes for the synthesis of naturally occurring chromenes related to aromatic hemiterpenes (Grundon 1978). One route exploits oxidative dehydrogenation at the benzylic site of a 2,2,6-trimethylchromene (for example, 2a) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to the corresponding formylchromene (2b), which was subsequently elaborated to 6-acetyl-2,2-dimethylchromene, a natural product called desmethoxy-enecalinalin (1b) (Venkama Naidu and Krishna Rao 1979). The other route makes use of Vilsmeier formylation of an appropriately activated chromene (for example, 2c) to afford 2,2-dimethyl-6-formyl-7-methoxychromene (2d), which was then converted to a group of three closely related naturally occurring aromatic hemiterpenes, enecalinalin (1a), enecalinalinol (secondary alcohol corresponding to 1a) and anhydroenecalinalinol (Venkama Naidu and Krishna Rao, 1979). Making use of the benzylic oxidation pathway, the synthesis of 6-acetyl-2,2-dimethyl-8-methoxychromene (1c) isolated from *Ageratina scorodonioides* (Bohlmann *et al* 1977) is now reported in this communication.

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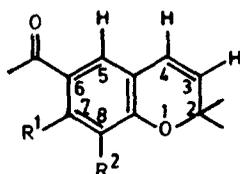
## 2. Results and discussion

### 2.1. Acetovanillochromene

6-Acetyl-2,2-dimethyl-8-methoxychromene (1c), reported (Bohlmann *et al* 1977) as a new natural product and its close relationship with enecalinal (1a) (Bjeldanes and Geissman 1969; Anthonsen 1969; Mukerjee *et al* 1970; Nakayama *et al* 1970), prompted us to furnish synthetic proof in support of the structure. However, survey of literature later revealed that its isolation was recorded earlier, although from a different source, *Eupatorium riparium*. It was named acetovanillochromene and was synthesized (Taylor and Wright 1971) from 4-acetyl-2-methoxyphenol (acetovanillone) (Reichstein 1927) via an acetylenic intermediate.

### 2.2. Synthesis of 6-acetyl-2,2-dimethyl-8-methoxychromene

8-Methoxy-2,2,6-trimethylchromene (2e) is the logical substrate for the synthesis of the natural product (1c) via benzylic oxidation, involving essentially the steps: Ar-CH<sub>3</sub> (2e) → Ar-CHO (2f) → Ar-CH(OH)CH<sub>3</sub> (2g) → Ar-COCH<sub>3</sub> (1c). The new chromene (2e) required for this purpose was prepared starting from 8-methoxy-6-methylcoumarin (3). The coumarin was in turn made from 2-methoxy-4-methylphenol (creosol) (4) (Schwarz and Hering 1963) by a standard procedure (Dey *et al* 1934) involving reaction of the phenol with malic acid in the presence of sulphuric acid. Grignard reaction of the coumarin (3) with excess methylmagnesium iodide gave the methoxy trimethylchromene (2e) which on reaction with DDQ in dioxan (Venkama Naidu and Krishna Rao 1979) gave the formylchromene (2f) in 68% yield. Repetition of Grignard reaction on 2f with methylmagnesium iodide gave the carbinol (2g) [isomeric analogue of the naturally occurring enecalinal (Bohlmann and Grenz 1977; Bohlmann and Jakupovic 1978)] which smoothly underwent dehydrogenation with manganese dioxide (Attenburrow *et al* 1952) to the titled natural product (1c). Vanillin failed to give the formylcoumarin (5) from which the carbinol (2g) could have been made in one step.



1a, R<sup>1</sup> = OCH<sub>3</sub>; R<sup>2</sup> = H

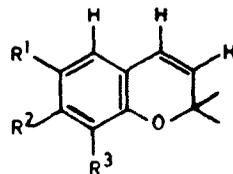
b, R<sup>1</sup> = R<sup>2</sup> = H

c, R<sup>1</sup> = H; R<sup>2</sup> = OCH<sub>3</sub>

2a, R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = R<sup>3</sup> = H

b, R<sup>1</sup> = CHO; R<sup>2</sup> = R<sup>3</sup> = H

c, R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = OCH<sub>3</sub>

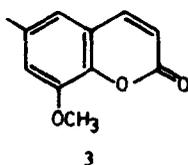


d, R<sup>1</sup> = CHO; R<sup>2</sup> = OCH<sub>3</sub>; R<sup>3</sup> = H

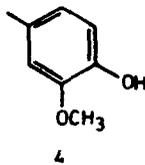
e, R<sup>1</sup> = CH<sub>3</sub>; R<sup>2</sup> = H; R<sup>3</sup> = OCH<sub>3</sub>

f, R<sup>1</sup> = CHO; R<sup>2</sup> = H; R<sup>3</sup> = OCH<sub>3</sub>

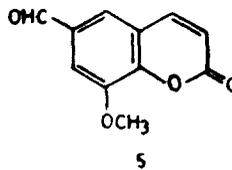
g, R<sup>1</sup> = CH(OH)CH<sub>3</sub>; R<sup>2</sup> = H; R<sup>3</sup> = OCH<sub>3</sub>



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### 3. Experimental

The instruments used for obtaining spectral data and details of general experimental technique employed are the same as those reported earlier (John and Krishna Rao 1978).

#### 3.1. 8-Methoxy-6-methylcoumarin (3)

2-Methoxy-4-methylphenol (creosol) (4) required for the preparation of the coumarin (3) was made from vanillin (Schwarz and Hering 1963), although in the present work much better yield (80%) of the product was obtained using large excess of toluene instead of ethanol as the medium of reaction.

Equimolar quantities of creosol (4) (13.8 g, 0.1 mol) and malic acid (13.4 g, 0.1 mol) were intimately mixed and heated to 120° with conc. H<sub>2</sub>SO<sub>4</sub> (25 ml). The reaction mixture began to froth up in a few minutes with evolution of CO<sub>2</sub>. When the gas evolution ceased (2 hr), the reaction mixture was cooled and the melt was poured into ice cold water (300 ml). The crude coumarin was extracted with ether (100 ml × 3). The ethereal extract was washed with water, aq. NaHCO<sub>3</sub> and aq. NaOH (5%) and finally with water to remove the unreacted acid and phenol. Evaporation of solvent gave the coumarin (3), mp 101° (methanol) (6.7 g, 35%); UV (EtOH) : λ<sub>max</sub> 221 (log ε 4.21), 256 (3.99) and 291 nm (4.10); IR (nujol) : ν<sub>max</sub> 1710 cm<sup>-1</sup> (C = O); <sup>1</sup>H-NMR : (60 MHz—CCl<sub>4</sub>) : δ (TMS) 2.38 (3H, s, Ar—CH<sub>3</sub>), 3.97 (3H, s, Ar—OCH<sub>3</sub>), 6.33 (1H, d, *J* 10Hz, H<sub>6</sub>), 6.85 (2H, d, *J* 3Hz, H<sub>5</sub> and H<sub>7</sub>) and 7.62 (1H, d, *J* 10Hz, H<sub>4</sub>) (Found : C, 69.24; H, 5.60. C<sub>11</sub>H<sub>10</sub>O<sub>3</sub> requires C, 69.46; H, 5.30%).

#### 3.2. 2,2-Dimethyl-6-formyl-8-methoxychromene (2f)

A solution of the coumarin (3) (3.8 g, 20 mmol) in dry ether (70 ml) was added to an ethereal solution (100 ml) of methylmagnesium iodide [prepared from magnesium (1.05 g, 44 mmol) and CH<sub>3</sub>I (8.52 g)] with stirring. The reaction mixture was maintained under reflux for 5 hr and left overnight at room temperature. It was then decomposed with aq. NH<sub>4</sub>Cl (5%, 200 ml) and extracted with ether (50 ml × 4). The methoxy trimethylchromene (2e) obtained on removal of the solvent was subjected to short-path distillation and used directly in the next reaction, b.t. 132°/3 mm (3.01 g, 74%); IR (neat) : ν<sub>max</sub> 1630 and 1490 cm<sup>-1</sup> (C = C and aromatic); <sup>1</sup>H-NMR (60 MHz — CCl<sub>4</sub>) : δ 1.22 [6H, s, —OC(CH<sub>3</sub>)<sub>2</sub>], 2.23 (3H, s, Ar — CH<sub>3</sub>), 3.75 (3H, s, OCH<sub>3</sub>), 5.70 (1H, d, *J* 12Hz, H<sub>3</sub>) 6.20 (1H, d, *J* 12Hz, H<sub>4</sub>) and 6.50 (2H, bs, H<sub>5</sub> and H<sub>7</sub>).

A mixture of the above chromene (2e) (2.04 g, 10 mmol) and DDQ (4.54 g, 20 mmol) in dioxan (35 ml) was heated under reflux for 70 hr. The resulting solid was filtered off. Removal of the solvent from the filtrate under reduced pressure gave a gummy residue which was filtered through a column of neutral alumina and the formylchromene (2f) was eluted out with benzene and further purified by short-path distillation, b.t. 158–160°/3 mm (1.5 g, 68%); UV (EtOH) : λ<sub>max</sub> 241 (log ε 4.19), 265 (4.20) and 315 nm (3.89); IR (neat) : ν<sub>max</sub> 2700, 2800 (H—C=O), 1680 (H—C=O), 1640, 1600 and 1580 cm<sup>-1</sup> (C=C and aromatic); <sup>1</sup>H-NMR (60 MHz—CCl<sub>4</sub>) : δ 1.45 [6H, s, —OC(CH<sub>3</sub>)<sub>2</sub>], 3.87, (3H, s, OCH<sub>3</sub>), 5.63 (1H,

d,  $J$  10Hz,  $H_3$ ), 6.33 (1H, d,  $J$  10Hz,  $H_4$ ), 7.03 (1H, d,  $J$  2Hz,  $H_7$ ), 7.20 (1H, d,  $J$  2Hz,  $H_5$ ) and 9.72 (1H, s,  $\underline{\text{CHO}}$ ) (Found : C, 71.03; H, 6.71.  $\text{C}_{12}\text{H}_{14}\text{O}_3$  requires C, 71.54; H, 6.47%).

### 3.3. 2,2-Dimethyl-6 $\alpha$ -hydroxyethyl-8-methoxychromene (2g)

A solution of the formylchromene (2f) (1.09 g, 5 mmol) in dry ether (20 ml) was added to a solution of methylmagnesium iodide [prepared from magnesium (0.12 g, 5 mmol) and  $\text{CH}_3\text{I}$  (1.42 g)] in dry ether (30 ml) with stirring. The reaction mixture was stirred at room temperature (5 hr), left overnight and poured into saturated aq.  $\text{NH}_4\text{Cl}$  (50 ml). The product was extracted with ether (40 ml  $\times$  3). Removal of the solvent and short-path distillation of the residue afforded the carbinol (2g) (1.0 g, 90%), b.t. 141–142°/3 mm; IR (neat) :  $\nu_{\text{max}}$  3200–3400 (b,  $\underline{\text{OH}}$ ), 1640, 1610 and 1590  $\text{cm}^{-1}$  (C=C and aromatic);  $^1\text{H-NMR}$  (60 MHz- $\text{CCl}_4$ ):  $\delta$  1.35 (3H, d,  $J$  8Hz,  $\text{CHCH}_3$ ), 1.40 [6H, s,  $-\text{OC}(\text{CH}_3)_2$ ], 1.67 (imp.), 2.73 (1H, b,  $\underline{\text{OH}}$ ), 3.72 (3H, s,  $\text{OCH}_3$ ), 3.80 (imp.), 4.47 (1H, m,  $\underline{\text{CHOH}}$ ), 5.53 (1H, d,  $J$  10 Hz,  $H_3$ ), 6.23 (1H, d,  $J$  10 Hz,  $H_4$ ), 6.48 (1H, d,  $J$  2Hz,  $H_7$ ) and 6.67 (1H, bs,  $H_5$ ) (Found : C, 72.03; H, 8.07.  $\text{C}_{14}\text{H}_{18}\text{O}_3$  requires C, 71.77; H, 7.74%).

### 3.4. 6-Acetyl-2,2-dimethyl-8-methoxychromene (1c)

A solution of the foregoing carbinol (2g) (0.5 g) in light petrol (30 ml) was stirred with a suspension of active manganese dioxide (2 g) for 2 hr. The solid was filtered off. Removal of solvent from the filtrate and purification by short-path distillation gave 1c (450 mg, 90%), b.t. 157–159°/3 mm; UV (EtOH) :  $\lambda_{\text{max}}$  245 (log  $\epsilon$  4.24), 265 (4.23) and 313 nm (3.79); IR (neat) :  $\nu_{\text{max}}$  1680 (C=O), 1605, 1580, 1480 (C=C and aromatic);  $^1\text{H-NMR}$  (60 MHz- $\text{CCl}_4$ ) : 1.45 [6H, s,  $-\text{OC}(\text{CH}_3)_2$ ], 2.43 (3H, s,  $\text{COCH}_3$ ), 3.83 (3H, s,  $\text{OCH}_3$ ), 5.60 (1H, d,  $J$  10Hz,  $H_3$ ), 6.28 (1H, d,  $J$  10Hz,  $H_4$ ), 7.17 (1H, d,  $J$  2Hz,  $H_7$ ) and 7.33 (1H, d,  $J$  2Hz,  $H_5$ ) (Found : C, 72.16; H, 6.70.  $\text{C}_{14}\text{H}_{16}\text{O}_3$  requires C, 72.39; H, 6.94%).

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