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AN ELEGANT SYNTHESIS OF SOME NATURALLY OCCURRING LINEAR ACETYLCHROMENES: EUPATORIOCHROMENE, METHYLEUPATORIOCHROMENE (ENCECALIN); EVODIONOL AND METHYLEVODIONOL

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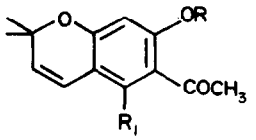
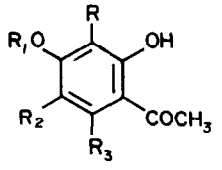
Abstract—An elegant synthesis of linear acetylchromenes, viz eupatoriochromene, methyleupatoriochromene (encecalin), evodionol and methylevodionol, has been achieved by blocking the reactive position C-3 of the appropriate ketones with an iodo group, prenylation with 3-chloro-3-methylbut-1-yne and subsequent cyclisation. Regiospecific introduction of C-prenyl group in the less reactive positon C-5 has been achieved by the reaction of the appropriate 3-iodo ketones with 2-methylbut-3-en-2-ol. The 5-prenyl ketones are also essential intermediates for the synthesis of linear acetylchromenes.

The occurrence of linear acetylchromenes, viz acetovanillochromene,[1] eupatoriochromene,[2] evodionol,[2-8] methyleupatoriochromene (encecalin),[2] and methylevodionol,[2,6,8-10] prompted us to devise a convenient method for the synthesis of such chromenes. These chromenes were earlier synthesised[11] by oxidative cyclisation of the appropriate C-prenyl derivatives with DDQ. The prenyl unit in ketones was introduced by their nuclear prenylation under acidic conditions[12] or BF_3-etherate[11,13,14] resulting in the formation of a complex mixture of mono- and di-C-prenylated derivatives along with a very small amount of O-prenyl derivative, the separation of the mixture was difficult and the overall yields poor. A convenient synthesis[15,16] of 2,2-dimethylchromenes involves condensation of a phenol with 3-chloro-3-methylbut-1-yne employing acetone/K_2CO_3 and cyclising the resulting propargyl ether with N,N-dimethylaniline. In this method if two ortho positions are free, the cyclisation takes place at the more reactive position.

In the present communication an elegant method has been devised for the synthesis of linear acetylchromenes by blocking the more reactive 3-position of ketones with an iodo group, prenylation with 3-chloro-3-methylbut-1-yne and subsequent cyclisation of the formed propargyl ether. Using this method synthesis of eupatoriochromene **1**, evodionol **2**, methyleupatoriochromene (encecalin) **3** and methylevodionol **4** has been effected.



	R	R_1
1	H	H
2	H	OCH_3
3	OCH_3	H
4	OCH_3	OCH_3



	R	R_1	R_2	R_3
5	I	H	H	H
6	I	$-C(CH_3)_2-C\equiv CH$	H	H
7	I	H	$-CH_2-CH=C(CH_3)_2$	H
8	H	H	$-CH_2-CH=C(CH_3)_2$	H
9	I	H	H	OCH_3
10	I	$-C(CH_3)_2-C\equiv CH$	H	OCH_3
11	I	H	$-CH_2-CH=C(CH_3)_2$	OCH_3
12	H	H	$-CH_2-CH=C(CH_3)_2$	OCH_3

Thus, prenylation of 2,4-dihydroxy-3-iodoacetophenone[17] **5** with 3-chloro-3-methylbut-1-yne in acetone in the presence of anhydrous K_2CO_3 and KI gave the 4-propargyl ether **6** which on heating with N,N-dimethyl aniline resulted in the formation of eupatoriochromene **1**. Its structure was in agreement with its NMR spectral data, which showed the presence of two singlets for C_3 and C_6 protons. It was identical with the specimen obtained by the earlier method.[13] The iodo group was displaced during cyclisation. This is a very convenient method for the formation of a chromene ring at the less reactive position. **1** was also prepared as follows. Treatment of **5** with 2-methylbut-3-en-2-ol in the presence of BF_3-etherate[13] gave 2,4-dihydroxy-3-iodo-5-prenylacetophenone **7**. It contained iodine and the NMR

spectrum a singlet for C_6 proton. Treatment of **7** with Zn–HCl in alcohol resulted in deiodination giving rise to the formation of 2,4-dihydroxy-5-prenylacetophenone[13] **8**. This method is unique for the regiospecific introduction of C-prenyl group in the less reactive position in ketones. Its cyclisation with DDQ gave **1**. Methylation of **1** with dimethyl sulphate in acetone in presence of anhydrous K_2CO_3 gave methyleupatoriochromene (encecalin) **3**.

Using the above method the synthesis of evodionol **2** and its methyl ether, methylevodionol **4** have also been effected. Thus 2,4-dihydroxy-3-iodo-6-methoxyacetophenone[18] **9** was reacted with 3-chloro-3-methylbut-1-yne in the presence of anhydrous K_2CO_3 and KI in acetone to give 2 - hydroxy - 3 - iodo - 4 - O - (1,1 - dimethylpropargyl) - 6 - methoxyacetophenone **10**, which on heating with N,N-dimethylaniline gave the required evodionol **2**. Its structure was in agreement with its NMR spectral data. **2** was also prepared as follows. **9** was treated with 2-methylbut-3-en-2-ol in presence of BR_3-etherate to give 2,4-dihydroxy-3-iodo-6-methoxy-5-prenylacetophenone **11** which on deiodination with Zn–HCl afforded 2,4-dihydroxy-6-methoxy-5-prenylacetophenone[6] **12**. Its cyclisation with DDQ yielded evodionol **2** in good yield. Methylation of **2** with dimethyl sulphate in acetone in presence of anhydrous K_2CO_3 gave methylevodionol **4**.

EXPERIMENTAL

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxychromene* (*eupatoriochromene*) **1**

Method (*i*)

2 - *Hydroxy* - 3 - *iodo* - 4 - O - (1,1 - *dimethylpropargyl*)*acetophenone* **6**. A solution of 2,4-dihydroxy-3-iodoacetophenone[17] **5** (1.0 g) in dry acetone (100 ml) was refluxed with 3-chloro-3-methylbut-1-yne (0.5 ml) in presence of anhydrous K_2CO_3 (4 g) and KI (0.5 g) for 20 hr. The insoluble potassium salts were filtered, residue washed with hot acetone and the combined filtrate distilled to yield a solid which on crystallisation from benzene gave colourless crystals (0.8 g), m.p. 100–101° (Found: C, 45.35; H, 3.78. $C_{13}H_{13}O_3I$ requires C, 45.36; H, 3.79%). NMR ($CDCl_3$) δ: 1.85 (s, 6H, $(CH_3)_2C\leftleftharpoons$); 2.65 (s, 3H, $-COCH_3$); 2.70 (s, 1H, $(CH_3)_2-C-C\equiv CH$); 7.24 (d, J = 10 Hz, 1H, H5); 7.72 (d, J = 10 Hz, 1H, H6); 13.40 (s, 1H, –OH chelated, exchangeable with D_2O).

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxychromene* (*eupatoriochromene*) **1**. 2 - Hydroxy - 3 - iodo - 4 - O - (1,1 - dimethyl propargyl)acetophenone **6** (1.0 g) was refluxed with N,N-dimethylaniline (5 ml) at 100–120° for 6 hr. The reaction mixture was cooled and poured into ice-cold hydrochloric acid. The separated solid was crystallized from benzene–petroleum ether to give **1** (0.4 g), m.p. 76–77° (lit[2]. 77–79°).

Method (*ii*)

2,4-*Dihydroxy*-5-*prenyl*-3-*iodoacetophenone* **7**. To a stirred solution of **5** (1.1 g) in dry dioxan (8 ml) was added gradually BF_3–Et_2O (0.3 ml) at 35–40°. To this was added a solution of 2-methylbut-3-en-2-ol (0.6 ml) in dry dioxan (5 ml) and the solution stirred for 1 hr at 35–40°. After dilution with ether (100 ml), the solution was washed with water (3 × 50 ml). The solution was extracted with 1% Na_2CO_3 aq. (3 × 50 ml) which on acidification gave unreacted **5** (0.7 g). The remaining ethereal solution was washed with water, dried ($MgSO_4$) and distilled. The solid product crystallized from alcohol to give colourless shining crystals of **7** (0.2 g), m.p. 135–37° (Found: C, 45.10; H, 4.35. $C_{13}H_{15}O_3I$ requires C, 45.09; H, 4.33%). NMR($CDCl_3$) δ: 1.90 & 2.0 (2s, 6H, $(CH_3)_2C=$), 2.53 (s, 3H, $-COCH_3$), 3.50 (d, J = 8 Hz, $-CH_2-CH=C(CH_3)_2$); 5.38 (m, 1H, $-CH_2-CH=C(CH_3)_2$); 7.40 (s, 1H, H6); 14.0 (s, 1H, –OH chelated, exchangeable with D_2O).

2,4 - *Dihydroxy* - 5 - *prenylacetophenone* **8**. A solution of 2,4-dihydroxy-5-C-prenyl-3-iodoacetophenone **7** (1.0 g) in alcohol (15 ml) was refluxed with zinc dust (0.5 g) and conc. hydrochloric acid (3 ml) for 30 min. The solution was filtered, evaporated and the separated product crystallized from benzene–petroleum ether as colourless plates (0.5 g) of **8** m.p. 144–45° (lit[13] 144–45°).

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxychromene* (*eupatoriochromene*) **1**. To a solution of **8** (0.5 g) in dry benzene (15 ml) DDQ (0.2 g) was added and the solution refluxed for 20 min on a water bath, resulting in the separation of colourless hydroquinone. The solution was filtered hot and the residue washed with benzene. Removal of the solvent gave the solid product which crystallized from benzene–petroleum ether to give **1** (0.4 g); m.m.p. 76–77°.

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *methoxychromene* (*encecalin*) **3**. The above chromene **1** (0.25 g) in dry acetone (50 ml) was refluxed for 12 hr with dimethyl sulphate (0.15 ml) in presence of anhydrous K_2CO_3 (1 g). The reaction mixture was filtered, inorganic salts washed with hot acetone and the combined filtrate evaporated to give **3** as an oil (lit[2] oil). NMR ($CDCl_3$) δ: 1.45 (s, 6H, $(CH_3)_2C=$); 2.52 (s, 3H, $-COCH_3$); 3.90 (s, 3H, $-OCH_3$); 5.55 (d, J = 10 Hz, H3); 6.32 (d, J = 10 Hz, H4); 6.40 (s, 1H, H8); 7.55 (s, 1H, H5).

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxy* - 5 - *methoxychromene* (*evodionol*) **2**

Method (*i*)

2 - *Hydroxy* - 3 - *iodo* - 4 - O - (1,1 - *dimethylpropargyl*) - 6 - *methoxy* - *acetophenone* **1**. A solution of 2,4 - dihydroxy - 3 - iodo - 6 - methoxy - acetophenone **9** (1.0 g) in dry acetone (100 ml) was refluxed with 3-chloro-3-methylbut-1-yne (0.4 ml) in presence of anhydrous K_2CO_3 (3 g) and KI (0.5 g) for 20 hr. Working up of the reaction mixture as in case of **6** gave a solid, which crystallized from benzene as colourless crystals (0.7 g), m.p. 110–111° (Found: C, 44.90; H, 4.30. $C_{14}H_{15}O_4I$ requires C, 44.92; H, 4.28%). NMR ($CDCl_3$) δ: 1.80 (s, 6H, $(CH_3)_2C\leftleftharpoons$); 2.65 (s, 1H, $-COCH_3$), 2.74 (s, 1H, $(CH_3)_2C-C\equiv CH$), 3.90 (s, 3H, $-OCH_3$); 6.95 (s, 1H, H5); 14.70 (s, 1H, –OH chelated exchangeable with D_2O).

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxy* - 5 - *methoxychromene* (*evodionol*) **2**. 2 - Hydroxy - 3 - iodo - 4 - O - (1,1 - dimethyl propargyl) - 5 - methoxy acetophenone **10** (1.0 g) was refluxed with N,N-dimethylaniline (5 ml) at 100–120° for 6 hr. The reaction mixture was cooled and poured into ice-cold hydrochloric acid. The solid obtained was crystallized from benzene–petroleum ether to give **2** (0.4 g), m.p. 85–86° (lit[2] 85°).

Method (*ii*)

2,4 - *Dihydroxy* - 5 - *prenyl* - 3 - *iodo* - 6 - *methoxyacetophenone* **11**. To a stirred solution of **9** (1.1 g) in dry dioxan (8 ml) was added gradually BF_3–Et_2O (0.3 ml) at 35–40°. To this was added a solution of 2-methylbut-3-en-2-ol (0.6 ml) in dry dioxan (5 ml) and the solution stirred for 1 hr. The reaction was worked up as for **7**. The product obtained was crystallized from alcohol as colourless needles **11** (0.15 g), m.p. 136–137°. (Found: C, 44.70; H, 4.55. $C_{14}H_{17}O_4I$ requires C, 44.68; H, 4.52%). NMR ($CDCl_3$) δ: 1.90 & 2.0 (2s, 6H, $(CH_3)_2C$ ); 2.60 (s, 3H, $-COCH_3$); 3.40 (d, J = 7 Hz, 2H, $(CH_3)_2=CH-CH_2$); 3.90 (s, 3H, $-OCH_3$); 5.25 (m, 1H, $(CH_3)_2C=CH-CH_2$); 14.50 (s, 1H, –OH chelated exchangeable with D_2O).

2,4 - *Dihydroxy* - 5 - *prenyl* - 6 - *methoxyacetophenone* **12**. A solution of 2,4 - dihydroxy - 5 - C - prenyl - 3 - iodo - 6 - methoxyacetophenone **11** (1.0 g) in alcohol (15 ml) was refluxed with zinc dust (0.5 g) and conc. hydrochloric acid (3 ml) for 30 min. The solution was filtered and evaporated. The product obtained was crystallized from benzene–petroleum ether to yield **12** as colourless plates (0.5 g) m.p. 127–28° (lit[6] 127–28°).

6 - *Acetyl* - 2,2 - *dimethyl* - 7 - *hydroxy* - 5 - *methoxychromene*(*evodionol*) **2**. To a solution of **12** (0.5 g) in dry benzene (15 ml) DDQ (0.2 g) was added and the solution refluxed for 30 min on a water bath resulting in the separation of colourless hydroquinone. The reaction was worked up as in case of **1**. Yield (0.4 g), m.m.p. 85–86°.

6 - *Acetyl* - 5,7 - *dimethyoxy* - 2,2 - *dimethylchromene* (*methylevodionol*) **4**. The above chromene **2** (0.25 g) in dry acetone (50 ml) was refluxed for 12 hr with dimethyl sulphate (0.15 ml) in presence of anhydrous K_2CO_3 (1 g). The reaction mixture was

filtered, inorganic salts washed with hot acetone and the combined filtrate evaporated to dryness and crystallized from ether–petroleum ether mixture to yield shining crystals of **4** (0.2 g), m.p. 76–77° (lit[2] 79°).

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