Al/Hg – mediated reductive dimerisation of 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran

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Aluminium amalgam – mediated reductive dimerisation of 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran produced two sets of diastereomeric bichromones coupled through 2,2' and 2,4'- positions; the latter set of diastereomers underwent diastereoconvergent dehydration to produce *Z*-3,3'-dimethoxycabonyl-3*H*-2,4'-bi[1-benzopyran-2-ylidene]-4-one.

Although a considerable number of naturally occuring bichromones have been isolated and synthesised in the past, most of them are connected through the phenyl rings.[1] Latterly, isolation of a few dimeric benzopyrans connected through the pyran rings has been reported. Bicoumarin from the seeds of *Colvillea racemosa*,[2] 4, 4'-dihydroxy-6, 6'-dimethoxy-3, 3'-bichromanone from the stem barks of *Kalopanax septemlobus*,[3] biflavones from roots of *Stellera chamaejasme* L[4] have been isolated. Synthesis of 3, 3'- and 2, 3'-bichromones,[5] synthesis of 4, 4'-biflavone[6] and 4, 4'-bicoumarin derivatives[7] by reductive coupling of flavone and 4-alkylcoumarins, respectively, synthesis of 3, 3'-, 3, 6'- and 3, 5'-bicoumarins by oxidative coupling,[8] synthesis of 3, 3'-bichromanone derivatives by Ni(0)-mediated Ullmann-type reaction[9] have all been accomplished. Anodic oxidation of some suitable enaminones for the synthesis of bichromones has also been reported.[10] Recently, synthesis of 2, 2'-bichromanones by sodium naphthalenide-induced reductive coupling of 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran **1** has been reported from our laboratory.[11] The low yield of the 2, 2'-bichromanones was mainly due to the high reactivity of sodium naphthalenide. The ester functions at the 3-position of the chromone rings have interacted further to produce a xanthone derivative.[11]

In an endeavour to synthesise cyclopentano[*b*]chromone skeleton, which is present in the natural products coniochaetone A and coniochaetone B,[12] we intended to get the 2, 2'-coupled product, whilst keeping the ester functions intact at the 3 and 3'-position of the chromone ring. Thus, a milder reducing agent Al-Hg, which allows the ester functions to survive, was the reagent of our choice. The results of the reaction of 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran **1** with Al-Hg in moist ether are reported herein.

Treatment of an ethereal solution of ester **1** with Al–Hg in moist ether at room temperature for 15 min produces **2–5** in overall good yield (Scheme 1). After stirring for 15 min at room temperature, the absence of starting ester **1** was observed

when monitored by TLC. The reaction mixture was filtered, concentrated and chromatographed over silica gel to obtain two sets of diastereomeric bichromones **2**, **3** and **4**, **5**, arising from the hydrodimerisation of **1**. The structures were assigned to be 2, 2'- and 2, 4'-bichromones and all the four isomeric products were found to exist in the enol-form from ¹H NMR spectral data. 2, 2'-Coupled products exist as *dl*-pair **2** (2RS, 2'RS) and *meso* **3**; 2, 4'-coupled products as **4** (2RS, 4'RS) and **5** (2RS, 4'SR). To the best of our knowledge this is the first example of a 2, 4'-coupled bichromone in the literature. One of the compounds **4c or 5c** could not be isolated from the reaction mixture of **1c**. From the study of ¹H NMR spectra, it was not possible to assign the diastereomers properly. During sodium naphthalenide-induced hydrodimerisation of **1**,[11] only one of the two diastereomers of 2, 2'-bichromone was isolated, except in one case. The isolated diastereomer was considered to be *meso* on the basis that the ester functions of the *dl* form reacted further to produce xanthone derivatives. By the present procedure both the diastereomers were isolated in a pure condition. Comparing the m.p.s of the diastereomers with that of the previously isolated product obtained from Na-naphthalenide induced reaction; it was observed that the m.p.s of the *dl* mixtures **2** are lower than that of *meso* forms **3**.

In an attempt to synthesise a cyclopentano[*b*]-1-benzopyran derivative, dimer **2** or **3**, was treated with NaOMe in methanol. However, either stirring at room temperature or heating under reflux for 6 h gives back the starting materials after acidification. Use of NaOMe in dry THF in place of MeOH in the previous procedure ends up with the same result.

Regarding the stereochemical assignment of 2, 4'-coupled products **4** and **5,** ¹H NMR spectral analyses were not sufficient. At first sight, the basic structure of the 2, 4'-coupled products **4** or **5**, inclined us to transform it into a spirochromone, a biologically active moiety,[13] by intramolecular *trans*-esterification between the OH-group at the 4'-position and the CO₂Me group at the 3-position. Heating a solution of **4a** or **5a** in dry methanol containing a catalytic amount of H₂SO₄ under
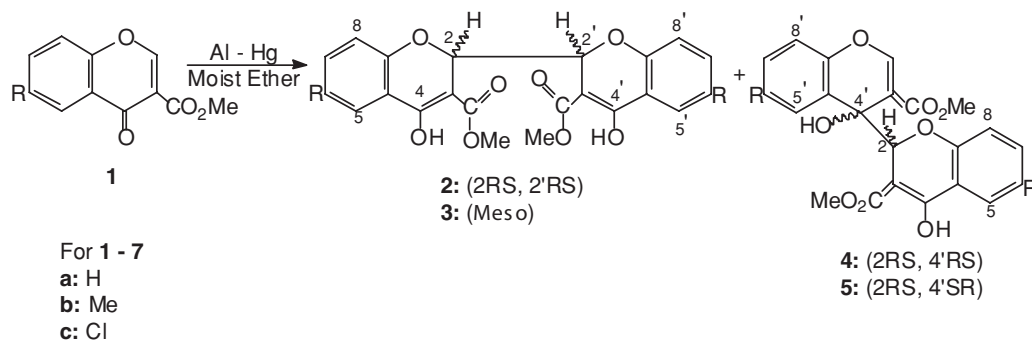
Scheme 1

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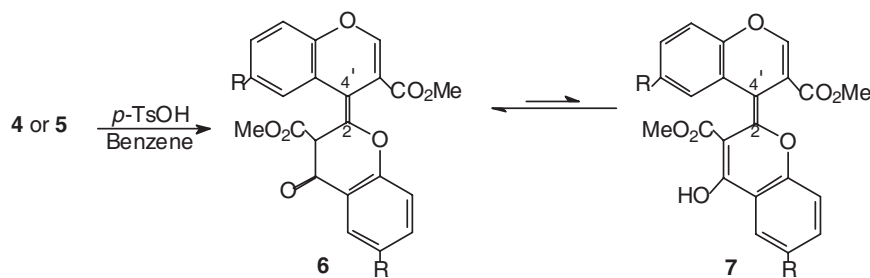
Scheme 2

reflux afforded a complex reaction mixture, but on heating for only 5 min in dry benzene containing a catalytic amount of *p*-toluene sulfonic acid, **4a** or **4b** undergoes dehydration to produce **6a** or **6b**, respectively, in excellent yield (Scheme 2). The interesting feature is that the other stereoisomer **5a** or **5b** also produces the same alkene **6a** or **6b**, respectively, but by heating under reflux for a little longer time (~15 min). The only alkene formed (**6**) is presumed to be the *Z*-isomer on the basis of ¹H NMR spectral data. All the methyl protons of the CO_2Me groups in **4** and **5** appear at ~δ 3.8 whereas, the methyl protons of one of the CO_2Me groups in **6** appears at ~δ 3.70, but the other at δ 4.05. This deshielding effect is due to the presence of the phenyl ring in the close vicinity of the CO_2Me group at the C-3 position of **6**. Formation of the only diastereomeric alkene rules out the possibility of an E^2-reaction, which should produce two diastereomeric alkenes. The E^1-pathway is favoured both due the tertiary nature of the alcohol and by the stabilisation of the carbocation by the pyran ring oxygen. As both the diastereomers **4** and **5** produce the same alkene **6**, so *syn*-elimination to one diastereomer and *anti*-elimination to other diastereomer have taken place. Considering the anti-elimination to be more favourable, compound **4**, which reacts relatively faster than **5**, may be presumed to undergo *anti*-elimination to give *Z*-alkene and **4** was assigned as 2RS, 4'RS.

An interesting observation is that the alkene **6** exists in the keto-form, not in the enol-form **7** as predicted from the ¹H NMR spectrum, though all its precursors **4** and **5** exist in the enol-form. This may be explained by considering the steric interaction between the phenyl ring of one chromone moiety and the CO_2Me group at the C-3 position of the other ring of **7** during its tendency to attain planarity to achieve the enol form. But, this steric interaction is alleviated when the CO_2Me group takes the pseudoequatorial position of the keto-form **6**. It is worth mentioning that in recent years many molecular machinery like chiroptical molecular switches and second generation molecular motors have been developed based on biphenanthrylidene,[14] naphthopyran-1'-ylidenethioxanthene[15] molecular moieties. 2, 4'-bi[1-benzopyran-2-ylidene]-4-one **6** or its naphthopyran derivatives may be utilised in making molecular machinery.

In conclusion, we have reported the synthesis of hitherto unreported 2, 4'-bichromone derivatives **4**, **5** and 2, 4'-bi [1-benzopyran-2-ylidene]-4-one **6** along with previously known 2, 2'-bichromones **2** and **3**. The stereochemistry of 2, 4'-bichromone was assigned on the basis of a diastereoconvergent dehydration experiment.

Experimental

Melting points reported are uncorrected. ¹H NMR spectra were recorded on a 300 MHz instrument in CDCl₃ solution with TMS as internal standard and IR spectra on a Perkin-Elmer 782 model in KBr. Light petroleum refers to the fraction with b.p. 60–80 °C.

*General procedure for the treatment of the ester **1** with aluminium amalgam*: A solution of the ester **1** (2 mmol) in moist ether (100 ml) was added all at a time to a suspension of aluminium amalgam [generated from aluminium foil (0.54 g, 20 mmol)] in moist ether (100 ml) at 20–25 °C. The reaction mixture was stirred at this temperature. The absence of the ester **1** was observed after 15 min when monitored by TLC. The reaction mixture was filtered and the residue was washed with ether. The washings and the filtrate were taken together and the ether was distilled out. The remaining solid was dissolved in CHCl₃ (20 ml), washed with water then dried (anhydrous Na₂SO₄) and chromatographed over silica gel (100–200 mesh), using light petroleum containing an increasing amount of benzene as eluent. The order of elution was diastereomers of 2, 2'-bi [1-benzopyran] **2** (*dl* pair), **3** (*meso*) then diastereomers of 2, 4'-bi [1-benzopyran] **4** and **5**.

(2RS, 2'RS)-2, 2'-bi[4-hydroxy-3-methoxycarbonyl-2H-1-benzo-pyran] (**2a**): White crystalline compound (80 mg, 20%); m.p. 181–182 °C (lit.,[11] m.p. 182 °C). Compound **2a** had superimposable IR with an authentic sample, which was wrongly considered as *meso*.[11]

(2RS, 2'RS)-2, 2'-bi[4-hydroxy-3-methoxycarbonyl-6-methyl-2H-1-benzopyran] (**2b**): White crystalline compound (80 mg, 18%); m.p. 178–180 °C; ν_max/cm⁻¹ 3100, 2950, 1665, 1620 cm⁻¹; δ_H 12.30 (2H, s, exchangeable, 2 × OH), 7.45 (2H, d, *J* = 1.9 Hz, 2 × 5-H), 6.95 (2H, dd, *J* = 8.3, 1.9 Hz, 2 × 7-H), 6.47 (2H, d, *J* = 8.3 Hz, 2 × 8-H), 5.28 (2H, s, 2 × 2-H), 3.77 (6H, s, 2 × OMe) and 2.30 (6H, s, 2 × 6-Me); Anal. Calcd. for C₂₄H₂₂O₈: C, 65.7; H, 5.1. Found: C, 65.4; H, 5.0.

(2RS, 2'RS)-2, 2'-bi[6-chloro-4-hydroxy-3-methoxycarbonyl-2H-1-benzopyran] (**2c**): White crystalline compound (50 mg, 10%); m.p. 220–221 °C; ν_max/cm⁻¹ 3150, 2925, 1650, 1620; δ_H 12.25 (2H, s, exchangeable, 2 × OH), 7.57 (2H, d, *J* = 2.5 Hz, 2 × 5-H), 7.17 (2H, dd, *J* = 8.8, 2.5 Hz, 2 × 7-H), 6.78 (2H, d, *J* = 8.8 Hz, 2 × 8-H), 5.01 (2H, s, 2 × 2-H) and 3.20 (6H, s, 2 × OMe); Anal. Calcd. for C₂₂H₁₆Cl₂O₈: C, 55.1; H, 3.4. Found: C, 55.4; H, 3.5.

Meso 2, 2'-bi[4-hydroxy-3-methoxycarbonyl-2H-1-benzopyran] (**3a**): White crystalline compound (70 mg, 17%); m.p. 200–202 °C (lit.,[11] m.p. 202 °C). Compound **3a** had superimposable IR with the authentic sample, which was wrongly considered as *dl* pair.[11]

Meso 2, 2'-bi[4-hydroxy-3-methoxycarbonyl-6-methyl-2H-1-benzopyran] (**3b**): White crystalline compound (85 mg, 19%); m.p. 196–198 °C (lit.,[11] m.p. 198 °C). Compound **3b** had superimposable IR with the authentic sample.[11]

Meso 2, 2'-bi[6-chloro-4-hydroxy-3-methoxycarbonyl-2H-1-benzo-pyran] (**3c**): White crystalline compound (110 mg, 23%); m.p. 236–238 °C; ν_max/cm⁻¹ 3150, 2920, 1650, 1620; δ_H 12.24 (2H, s, exchangeable, 2 × OH), 7.58 (2H, d, *J* = 2.5 Hz, 2 × 5-H), 7.00 (2H, dd, *J* = 8.7, 2.5 Hz, 2 × 7-H), 6.25 (2H, d, *J* = 8.7 Hz, 2 × 8-H), 5.29 (2H, s, 2 × 2-H) and 3.87 (6H, s, 2 × OMe); Anal. Calcd. for C₂₂H₁₆Cl₂O₈: C, 55.1; H, 3.4. Found: C, 55.3; H, 3.6.

(2RS, 4'RS)-4, 4'-dihydroxy-3, 3'-dimethoxycarbonyl-2H, 4'H-2, 4'-bi[1-benzopyran] (**4a**): White crystalline compound (85 mg, 21%); m.p. 164 °C; ν_max/cm⁻¹ 3404, 2951, 1676, 1647, 1443, 1308, 1286; δ_H 12.41 (1H, s, exchangeable, 4-OH), 7.92 (1H, s, 2'-H), 7.45 (1H, m, 5-H), 7.16 (1H, dd, *J* = 7.7, 1.7 Hz, 5'-H), 7.06 (1H, m, 7-H), 6.97 (1H, m, 7'-H), 6.93 (1H, m, 8-H), 6.63 (1H, m, 6-H), 6.59 (1H, dd, *J* = 8.0, 1.0 Hz, 8'-H), 6.53 (1H, m, 6'-H), 5.62 (1H, s, 2-H), 5.10 (1H, s, 4'-OH), 3.87 (3H, s, 3-CO₂Me) and 3.82 (3H, s, 3'-CO₂Me); Anal. Calcd. for C₂₂H₁₈O₈: C, 64.4; H, 4.4. Found: C, 64.7; H, 4.5.

(2RS, 4'RS)-4, 4'-dihydroxy-3, 3'-dimethoxycarbonyl-6, 6'-dimethyl-2H, 4'H-2, 4'-bi[1-benzopyran] (**4b**): White crystalline compound (70 mg, 16%); m.p. 170–172 °C; ν_max/cm⁻¹ 3466, 2957, 1685, 1643, 1578, 1491, 1275; δ_H 12.36 (1H, s, exchangeable, 4-OH), 7.88 (1H, s, 2'-H), 7.25 (1H, d, *J* = 2.1 Hz, 5-H), 6.97 (1H, d, *J* = 2.0 Hz, 5'-H), 6.86 (1H, dd, *J* = 8.1, 2.1 Hz, 7-H), 6.75 (1H, dd, *J* = 8.1, 2.0 Hz, 7'-H), 6.48 (1H, d, *J* = 8.1 Hz, 8-H), 6.42 (1H, d, *J* = 8.1 Hz, 8'-H), 5.56 (1H, s, 2-H),

5.12 (1H, s, exchangeable, 4'-OH), 3.84 (3H, s, 3-CO$_2$Me), 3.80 (3H, s, 3'-CO$_2$Me), 2.23 (3H, s, 6-Me) and 2.10 (3H, s, 6'-Me); Anal. Calcd. for C$_{24}$H$_{22}$O$_8$: C, 65.7; H, 5.1. Found: C, 65.3; H, 5.4.

6, 6'-Dichloro-4, 4'-dihydroxy-3, 3'-dimethoxycarbonyl-2H, 4'H-2, 4'-bi[1-benzopyran] (**4c** or **5c**): White crystalline compound (25 mg, 5%); m.p. 196–198 °C; ν_{max}/cm^{-1} 3410, 2950, 1680, 1620, 1400; δ_H 12.36 (1H, s, exchangeable, 4-OH), 7.88 (1H, s, 2'-H), 7.42 (1H, d, *J* = 2.5 Hz, 5-H), 7.25 (1H, d, *J* = 2.5 Hz, 5'-H), 7.03 (1H, dd, *J* = 8.6, 2.5 Hz, 7-H), 7.00 (1H, dd, *J* = 8.7, 2.5 Hz, 7'-H), 6.54 (1H, d, *J* = 8.6 Hz, 8-H), 6.25 (1H, d, *J* = 8.7 Hz, 8'-H), 5.57 (1H, s, 2-H), 5.15 (1H, s, exchangeable, 4'-OH), 3.87 (3H, s, 3-CO$_2$Me) and 3.83 (3H, s, 3'-CO$_2$Me); Anal. Calcd. for C$_{22}$H$_{16}$Cl$_2$O$_8$: C, 55.1; H, 3.4. Found: C, 55.5; H, 3.3.

(2RS, 4'SR)-4, 4'-dihydroxy-3, 3'-dimethoxycarbonyl-2H, 4'H-2, 4'-bi[1-benzopyran] (**5a**): White crystalline compound (65 mg, 16%); m.p. 162 °C; ν_{max}/cm^{-1} 3400, 2948, 1675, 1635, 1440, 1300, 1280; δ_H 12.37 (1H, s, exchangeable, 4-OH), 7.57 (1H, dd, *J* = 7.6, 1.8 Hz, 5-H), 7.53 (1H, s, 2'-H), 7.46 (1H, dd, *J* = 7.5, 1.0 Hz, 5'-H), 7.25 (1H, m, 7-H), 7.20 (1H, m, 7'-H), 6.99 (1H, m, 8-H), 6.84 (1H, m, 6-H), 6.68 (1H, dd, *J* = 8.0, 1.2 Hz, 8'-H), 6.59 (1H, m, 6'-H), 5.71 (1H, s, 2-H), 5.37 (1H, s, exchangeable, 4'-OH), 3.82 (3H, s, 3-CO$_2$Me) and 3.57 (3H, s, 3'-CO$_2$Me); Anal. Calcd. for C$_{22}$H$_{18}$O$_8$: C, 64.4; H, 4.4. Found: C, 64.1; H, 4.2.

(2RS, 4'SR)-4, 4'-dihydroxy-3, 3'-dimethoxycarbonyl-6, 6'-dimethyl-2H, 4'H-2, 4'-bi[1-benzopyran] (**5b**): White crystalline compound (75 mg, 17%); m.p. 156–158 °C; ν_{max}/cm^{-1} 3460, 2950, 1680, 1628, 1575, 1490, 1270; δ_H 12.35 (1H, s, exchangeable, 4-OH), 7.54 (1H, s, 2'-H), 7.32 (1H, d, *J* = 1.9 Hz, 5-H), 7.21 (1H, d, *J* = 1.6 Hz, 5'-H), 7.06 (1H, dd, *J* = 8.3, 1.9 Hz, 7-H), 6.96 (1H, dd, *J* = 8.3, 1.6 Hz, 7'-H), 6.86 (1H, d, *J* = 8.3 Hz, 8-H), 6.62 (1H, d, *J* = 8.3 Hz, 8'-H), 5.67 (1H, s, 2-H), 5.37 (1H, s, exchangeable, 4'-OH), 3.82 (3H, s, 3-CO$_2$Me), 3.59 (3H, s, 3'-CO$_2$Me), 2.23 (3H, s, 6-Me) and 2.16 (3H, s, 6'-Me); Anal. Calcd. for C$_{24}$H$_{22}$O$_8$: C, 65.7; H, 5.1. Found: C, 65.4; H, 5.0.

*Treatment of **4** and **5** with p-toluene sulfonic acid*: A solution of **4** or **5** (0.1mmol) and a catalytic amount of *p*-toluene sulfonic acid (5 mg) in dry benzene was heated under reflux for 5 min and 15 min for **4** and **5**, respectively. The reaction mixtures were washed with water, dried over sodium sulfate and concentrated to produce the same compound 2, 3-dihydro-3, 3'-dimethoxycarbonyl-4*H*, 4'*H*-2, 4'-bi[1-benzopyran-2-ylidene]-4-one **6** with quantitative yield for both cases.

*Compound **6a***: White crystalline compound, m.p. 192–194 °C; ν_{max}/cm^{-1} 2953, 1724, 1713, 1660,1464, 1315, 1232, 1093; δ_H 8.16 (1H, dd, *J* = 7.9, 1.5 Hz, 5-H), 7.95 (1H, s, 2'-H), 7.62–7.56 (2H, m, ArH), 7.36 (1H, m, ArH), 7.30–7.25 (2H, m, ArH), 7.15–7.10 (2H, m, ArH), 5.47 (1H, s, 3-H), 4.05 (3H, s, 3-CO$_2$Me) and 3.71 (3H, s, 3'-CO$_2$Me); Anal. Calcd. for C$_{22}$H$_{16}$O$_7$: C, 67.4; H, 4.1. Found: C, 67.6; H, 3.9.

*Compound **6b***: White crystalline compound, m.p. 202–203 °C; ν_{max}/cm^{-1} 3018, 2918, 1720, 1715, 1651, 1485, 1213; δ_H 7.94 (1H, d, *J* = 2.1 Hz, 5-H), 7.92 (1H, s, 2'-H), 7.39 (1H, dd, *J* = 8.6, 2.1 Hz, 7-H), 7.35 (1H, d, *J* = 1.6 Hz, 5'-H), 7.16 (1H, d, *J* = 8.6 Hz, 8-H), 7.06 (1H, dd, *J* = 8.3, 1.6 Hz, 7'-H), 6.99 (1H, d, *J* = 8.3 Hz, 8'-H), 5.41 (1H, s, 3-H), 4.05 (3H, s, 3-CO$_2$Me), 3.70 (3H, s, 3'-CO$_2$Me), 2.40 (3H, s, 6-CH$_3$) and 2.27 (3H, s, 6'-CH$_3$) Anal. Calcd. for C$_{24}$H$_{20}$O$_7$: C, 68.6; H, 4.8. Found: C, 68.4; H, 4.9.

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