

Cyclisation of 3-[cyclopent-2-enyl]-4-hydroxy[1]benzopyran-2-one[†]

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3-[Cyclopent-2-enyl]-4-hydroxy[1]benzopyran-2-one **3** has been prepared by the reaction of 3-chlorocyclopent-2-ene **2** and 4-hydroxy[1]benzopyran-2-one **1**. Compound **3** or its acetate **4** on treatment with pyridine hydrotribromide in dichloromethane at 0-5°C for 2 hr gives fused furo chromone **5** in 90 % yield. Compound **5** on refluxing in 50 % sulphuric acid rearranges to the fused furocoumarin **7** in 87 % yield.

Coumarin¹ and its derivatives² are important compounds due to their physiological activity. The biological activity^{3, 4} of 4-alkyl- and 3-alkylcoumarins has made their synthesis⁵ interesting. During our work on the synthesis of fused bicyclic coumarins⁶ we encountered some interesting observations which we report here.

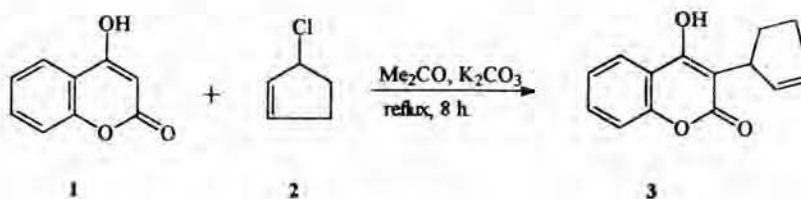
3-[Cyclopent-2-enyl]-4-hydroxy[1] benzopyran-2-one **3**, the starting material for this study, was easily prepared as a crystalline solid m.p 134°C in 50% yield from the reaction of 4-hydroxy[1]benzopyran-2-one⁷ **1** and 3-chlorocyclopentene⁸ **2** in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme I).

Results and Discussion

Two approaches for the cyclisation of 3-[cyclopent-2-enyl]-4-hydroxy[1]benzopyran-2-one were considered. The first one was through a sequence of reactions⁹: (i) conversion of the hydroxy to acetate, and derivative, (ii) addition of bromine to cyclopentenyl double bond of the acetate (iii) treatment of the dibromide with refluxing ethanolic potassium hy-

droxide. The compound **3** on treatment with acetic anhydride and freshly fused sodium acetate furnished the solid acetate derivative **4** in 90 % yield. However, the reaction of the acetate derivative with bromine in acetic acid gave a mixture which we could not effectively separate. So we attempted to use a somewhat milder reagent pyridine hydrotribromide for this cyclisation. The acetate **4** was treated with pyridine hydrotribromide in dichloromethane at 0-5°C for 2 hr to give a crystalline solid in 90% yield. This was also obtained in 89% yield when compound **3** was directly treated with pyridine hydrotribromide under the same reaction condition, (Scheme II). This product **5** resisted loss of HBr when refluxed with 5% ethanolic KOH or 2,4,6-collidine in chloroform for 3 hr or anhydrous potassium carbonate in acetone. Structure **5** was assigned for this product on the basis of its elemental analysis and spectral data (*vide* Experimental). The formation of chromone skeleton is clearly indicated by the IR absorption band at 1650 cm⁻¹ and ¹H-NMR signal, a doublet of a doublet (1H, C₆-H) at δ 8.20-8.40.

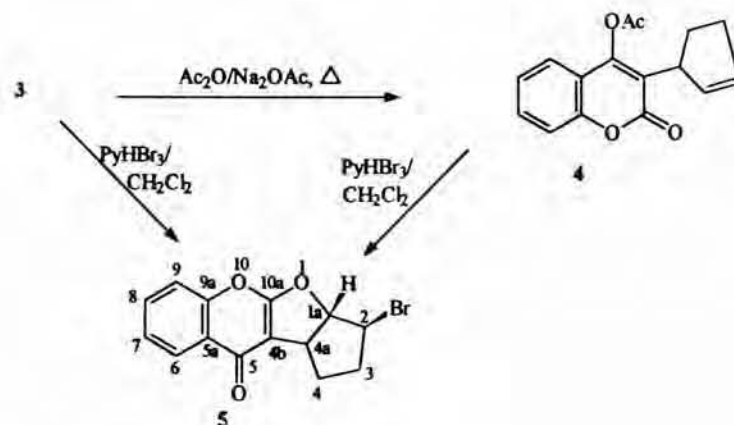
A possible pathway for the formation of chromone



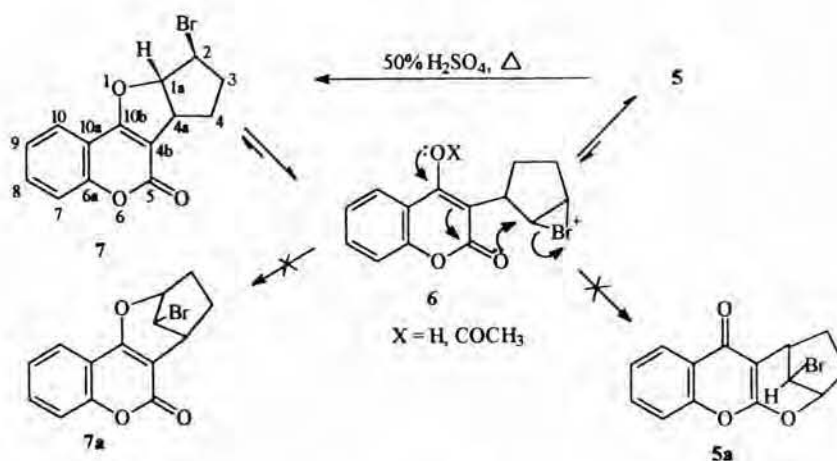
Scheme I

[†] For a preliminary report see ref. 15.

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Scheme II



Scheme III

5 from 3 or acetate 4 may involve formation of an intermediate bromonium ion 6 followed by 5-exo cyclisation to give the chromone derivative 5 (Scheme III). Chromone 5, if refluxed in 50% sulphuric acid for 8 hr, rearranges to the coumarin derivative 7, yield 87%, m.p 135°C . The conversion of chromone 5 to coumarin 7 is clearly indicated by the IR absorption band at 1720 instead of 1650 cm^{-1} (in 5) and the shift of the low field 1H double doublet centred at δ 8.30 in 5 to high field in 7. It seems that the lactone form is more stable in acid than the γ -pyrone form.

There are two possible pathways through which the intermediate bromonium ion 6, can cyclise, *via* the nucleophilic attack by the oxygen at the C-2' of the cyclopentenyl side chain (5-exo cyclisation) may give the fused furo derivative 5, 7 or the nucleophilic attack at the C-3' of the cyclopentenyl side chain (6-endo cyclisation) would provide the bridged bicyclic

derivative 5a, 7a. 6-endo-Cyclisation to give 5a and 7a may not be an allowed process of Baldwin's rule.¹⁰ However, the assignment of structures for the products from the available spectral data proved inconclusive. Accordingly the single crystal X-ray analyses¹¹ of these products were carried out to definitely establish their structures. Alternative structures 5a and 7a for the products were discarded on the basis of the X-ray data¹⁵. Pluto structures of the products 5 and 7 are shown in Figures 1 and 2, respectively. Product 5 is kinetically controlled and is formed exclusively. Thermodynamic product 7 is obtained only by acid-catalysed rearrangement of 5.

It is interesting to note that the bromonium ion intermediate 8, derived from the reaction of *o*-cyclohexenylphenols and pyridine hydrotribromide¹² or hexamethylene hydrotribromide¹³, cyclises exclusively to the bridged bicyclic product 9 (Scheme IV).

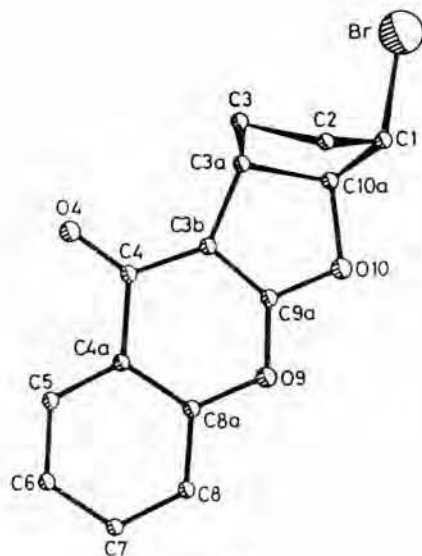


Figure 1

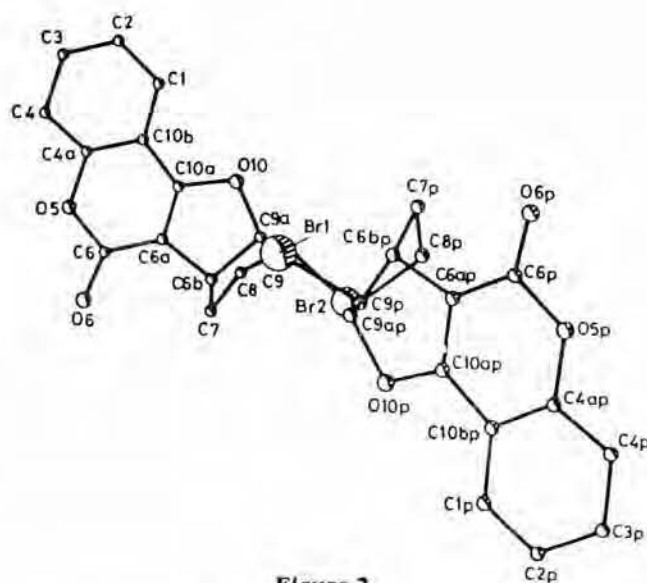


Figure 2

However, the corresponding 3-(2-cyclohexenyl)-4-acetoxycoumarin **10** on treatment with pyridine hydrotribromide in dichloromethane at 0-5°C for 2 hr gave mostly the tribromo derivative¹⁴ **12** (Scheme V).

Cyclisation of the proposed intermediate **6** is facile under such a mild condition perhaps due to favourable juxtaposition of the reacting functionalities to furnish a stable cyclic furochromone **5**. The failure of compound **10** to give the corresponding bicyclic derivative is attributable to the fact that the preferred conformation with bulky 3-coumarinyl moiety in equatorial orientation does not provide nucleophilic -OH group in proximity with carbon bearing the nucleophobic Br.

The cyclisation of substrate **3** to chromone **5** pre-



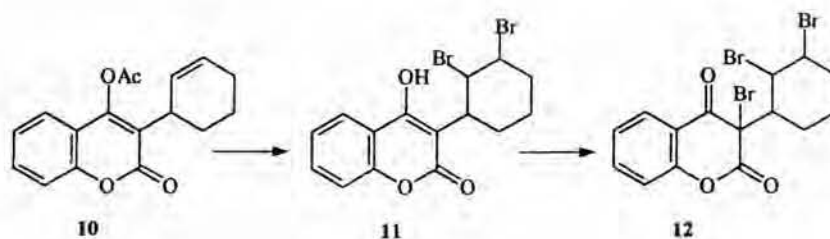
Scheme IV

sented here is simple and regioselective. The transformation of chromone **5** to coumarin **7** is unusual and noteworthy.

Experimental Section

General. Melting points are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 spectrophotometer (λ_{max} in nm) and IR spectra in KBr discs on a Perkin-Elmer 1330 apparatus (ν_{max} in cm^{-1}). ^1H NMR spectra were run in CDCl_3 with SiMe_4 as internal standard on a Jeol Fx-100 (100 MHz) instrument at the Indian Institute of Chemical Biology, Calcutta and on a Bruker 400 (400 MHz) instrument at the University of Alberta, Edmonton (chemical shifts in δ ppm). Single crystal X-ray analyses were carried out at the Indian Institute of Science, Bangalore. Elemental analyses and mass spectra were recorded by RSIC (CDRI), Lucknow. Silica gel (60-120 mesh) was obtained from Qualigen and aluminium oxide (basic) from SRL. Extracts were dried over anhydrous sodium sulphate.

Preparation of 3-[cyclopent-2-enyl]-4-



Scheme V

hydroxy[1]benzopyran-2-one 3. 4-Hydroxycoumarin **1**; (6.5 g, 40 mmoles), 3-chlorocyclopentene (**2**; 5 g, 50 m mole) and anhydrous potassium carbonate (6 g, excess) was refluxed in acetone (250 mL) on a water-bath for 2 hr. The reaction mixture was cooled and filtered. The solvent was removed and the residue was extracted with ether (3×50 mL), and the ether extract washed with sodium bicarbonate solution (5 %, 2×50 mL), brine (2×50 mL) and dried (Na_2SO_4). Removal of ether gave a crude mass which was chromatographed over silica gel (60-120 mesh). The product **3** was obtained when the column was eluted with benzene-pet. ether (bp 60-80°C) (1:1), yield 50%; mp 134°C; UV: 272 (log ϵ 3.94), 284 (log ϵ 3.97), 310 (log ϵ 3.91); IR: 3120 (broad), 2900, 1700, 1630; ^1H NMR: δ 2.40-2.96 (m, 4H), 4.24-4.60 (m, 1H), 6.00-6.40 (m, 2H), 7.24-7.60 (m, 4H), 7.72-7.88 (dd, 1H, $J = 8.5, 1.5$ Hz); MS: 228 (M^+). Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_3$ C, 73.68; H, 5.26%. Found: C, 73.60; H, 5.47%.

Preparation of acetate derivative 4 of compound

3. A mixture of the hydroxy compound **3** (1.14 g, 5 mmoles) and freshly fused sodium acetate (0.2 g) was heated in acetic anhydride (10 mL) on a waterbath for 5 hr. The reaction mixture was cooled and poured into ice-water, stirred well when an insoluble solid was obtained. This was recrystallised from chloroform-pet. ether (60-80°C) to give a white crystalline solid **4**, yield 90%, mp 114°C; UV: 274 (log ϵ 4.25), 314 (log ϵ 4.07); IR: 2980, 1790, 1740, 1650, 1210; ^1H NMR: δ 2.36 (s, 3H), 2.36-2.80 (m, 4H), 4.04-4.40 (m, 1H), 5.64-6.12 (m, 2H), 7.24-7.60 (m, 4H); MS: m/z 270 (M^+), 228 (base peak), 227. Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_4$ C, 71.11; H, 5.18%. Found: C, 71.39; H 5.33%.

Cyclisation of 3-cyclopent-2-enyl-4-acetoxy[1]-benzopyran-2-one 4. The solid pyridine hydrotribromide (1.28 g, 4 mmoles) was added to a solution of the acetate **4** (1.08 g, 4 mmoles) in dichloromethane (55 mL). The reaction mixture was stirred for 2 hr on a magnetic stirrer at 0-5°C. Dichloromethane (50 mL) was added to the red coloured solution. This was then washed with dilute sodium bicarbonate solution (3×20 mL), water (3×20 mL) and dried (Na_2SO_4). The solvent was removed and the crude solid was recrystallised from chloroform-hexane, to give **5**, yield 90%; mp 130°C; UV: 240 (log ϵ 3.95), 284 (log ϵ 4.15); IR: 2990, 1650 ($>\text{C}=\text{O}$), 1580; ^1H NMR: δ 2.04-2.60 (m, 4H), 4.04-

4.40 (dt, 1H, $J = 1.2, 8$ Hz), 4.48-4.68 (br s, 1H), 5.44-5.68 (d, 1H, $J = 8$ Hz), 7.32-7.80 (m, 3H, Ar-H), 8.20-8.40 (dd, 1H, $J = 8.5, 1.5$ Hz, Ar-H); ^{13}C NMR: δ 174.7 (C-5), 167.7 (C-10a), 153.3 (C-9a), 132.6 (C-8), 125.7 (C-6), 125.6 (C-7), 123.8 (C-5a), 117.3 (C-9), 97.1 (C-1a), 94.5 (C-4b), 52.3 (C-2), 41.6 (C-4a), 33.2 (C-4), 29.1 (C-3); MS: 308, 306 (M^+), 227 (M-Br), 226 (base peak). Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{O}_3\text{Br}$ C, 54.90; H, 3.59%. Found: C, 54.96; H, 3.35%.

Conversion of chromone 5 to coumarin 7 with sulphuric acid. The chromone **5** (0.9 g, 3 mmoles) was heated in 50% sulphuric acid (9 mL) on a water-bath for 8 hr. The reaction mixture was poured into ice-cold water (50 mL) and extracted with chloroform (3×50 mL). The chloroform extract was washed with 5% sodium bicarbonate solution (3×20 mL), water (3×20 mL) and dried (Na_2SO_4). Removal of solvent gave a solid mass which was recrystallised from chloroform-pet. ether (bp 40-60°C) to give the product **7**, yield 87%, mp 135°C; UV: 240 (log ϵ 3.70), 277 (log ϵ 3.97), 289 (log ϵ 4.08), 314 (log ϵ 4.07), 328 (log ϵ 3.93); IR: 2990, 1720 ($>\text{C}=\text{O}$); ^1H NMR: δ 2.04-2.60 (m, 4H), 4.00-4.20 (t, 1H, $J = 8$ Hz), 4.52-4.68 (d, 1H, $J = 3$ Hz), 5.60-5.76 (d, 1H, $J = 8$ Hz), 7.30-7.80 (m, 4H, Ar-H); ^{13}C NMR: δ 165.5 (C-10b), 160.1 (C-5), 154.9 (C-6a), 132.6 (C-8), 124.0 (C-9), 122.7 (C-10), 116.9 (C-7), 111.9 (C-10a), 104.9 (C-4b), 97.5 (C-1a), 53.0 (C-2), 43.5 (C-4a), 33.3 (C-4), 29.1 (C-3); MS: m/z 308, 306 (M^+), 227 (M-Br), 226 (base peak). Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{O}_3\text{Br}$ C, 54.90; H, 3.59%. Found: C, 54.87; H, 3.63%.

Acknowledgement

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