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Reactivity of Isocoumarins. I. Effect of a Neighboring Hydroxyl Group on the Reduction of the Lactone Carbonyl Group

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The reduction of 3,4-dihydroisocoumarins (**1**, **3**, **6**, **11a**, **11b**, and **12b**) having a hydroxyl group or acetoxyl group at the C₈-position adjacent to the lactone carbonyl group with lithium aluminum hydride gave novel products, 1,8-dihydroxyisochromans (**10a**, **13**, and **16a**), in addition to 8-hydroxyisochromans (**2**, **8**, and **14**) and 2-(3-hydroxy-2-hydroxymethylphenyl)ethanols (**4**, **9**, and **15**). The isochromans and 2-(2-hydroxymethylphenyl)ethanols are known reduction products of 3,4-dihydroisocoumarins lacking a C₈-hydroxyl group. In addition, **13** was obtained selectively in 50% yield by reduction of the magnesium chelate of **11a** with lithium aluminum hydride. Similarly, 8-hydroxy-3-phenylisocoumarin (**23a**) and 8-acetoxy-3-phenylisocoumarin (**23b**) both gave 2-formyl-3-hydroxybenzyl phenyl ketone (**24**). Based on these results, a mechanism for the reduction of 8-hydroxy-3,4-dihydroisocoumarins is proposed, as shown in Chart 3.

Keywords—reduction of lactone; 1-hydroxyisochroman; 3,4-dihydroisocoumarin; isocoumarin; chelating compound; effect of neighboring group

In the course of a study²⁾ on the structure-sweetness relationship of 3,4-dihydroisocoumarins, an attempt was made to prepare 8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**2**) by reduction of phyllodulcin [8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydroisocoumarin] (**1**). Diacetylphyllodulcin (**3**) was treated in place of **1** with lithium aluminum hydride in dry ether, **1** being only slightly soluble in ether. After completion of the reduction of **3**, the resulting mixture was refluxed with ethanol for recrystallization, followed by column chromatographic separation on silica gel. 1-Ethoxy-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**5**),³⁾ **2**, and 1-(3-hydroxy-4-methoxyphenyl)-2-(3-hydroxy-2-hydroxymethylphenyl)ethanol (**4**) were obtained in 47%, 8%, and 10% yields, respectively.

Similar results were obtained in the reduction of diacetylhydrangenol [8-acetoxy-3-(4-acetoxyphenyl)-3,4-dihydroisocoumarin] (**6**): Treatment of **6** with lithium aluminum hydride gave 1-ethoxy-3-(4-hydroxyphenyl)-8-hydroxyisochroman (**7**),³⁾ 8-hydroxy-3-(4-hydroxyphenyl)isochroman (**8**), and 1-(4-hydroxyphenyl)-2-(3-hydroxy-2-hydroxymethylphenyl)ethanol (**9**).

Although the formation of 2-(2-hydroxymethylphenyl)-1-phenylethanol by reduction of 3-phenyl-3,4-dihydroisocoumarin with lithium aluminum hydride has already been reported by Bendall and Dharamshi,⁴⁾ the formation of 1-ethoxyisochromans (**5** and **7**) by similar reduction of 3,4-dihydroisocoumarins (**1**, **3**, and **6**) has not been reported, and we were interested in the reaction mechanism of this reduction.

In high-performance liquid chromatography (HPLC) of the reaction mixture obtained by reduction of **3** with lithium aluminum hydride, three peaks appeared. Two were identical with

- 1) Location: a) *Tsushima-naka 1-1-1, Okayama 700, Japan*; b) *Tamagawa-cho, Minamiku, Fukuoka 815, Japan*.
- 2) M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, N. Yoshida, and T. Koyama, *Yakugaku Zasshi*, **92**, 367 (1972).
- 3) The starting materials (**1**, **3**, and **6**) employed for reduction were all racemic compounds, and the resulting 1-ethoxyisochromans (**5** and **7**) had no optical activity.
- 4) V.I. Bendall and S.S. Dharamshi, *J. Chem. Soc. Perkin Trans. I*, **1972**, 2732.

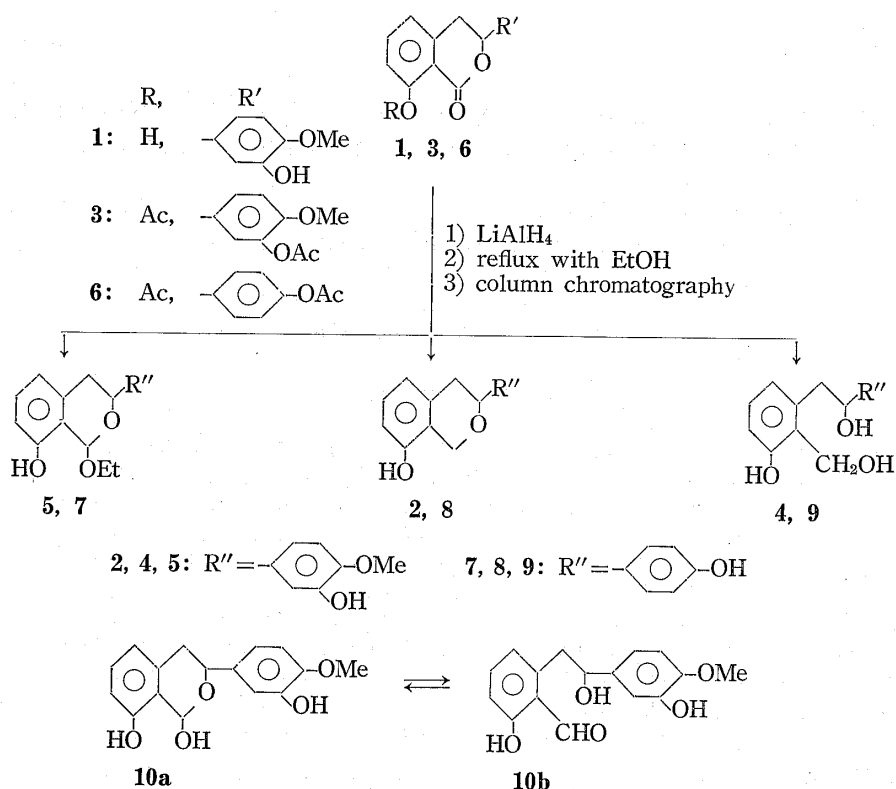


Chart 1

those of authentic samples of **2** and **4**, but the remaining one did not coincide with that of authentic **5**. However, when the reduction mixture was refluxed with ethanol, a peak of **5** appeared and the unknown peak disappeared.

On purification of the mixture obtained by reduction of **3** with lithium aluminum hydride by column chromatography, compound **10** was obtained. The nuclear magnetic resonance (NMR) spectrum of **10** showed two singlet peaks at δ : 5.56 and 10.20, which did not disappear on addition of D_2O . The ratio of the heights of the two peaks was 2:1. Elemental analysis and NMR data for **10** suggested it to be a mixture of tautomers, 1,8-dihydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**10a**) and 2-(2-formyl-3-hydroxyphenyl)-1-(3-hydroxy-4-methoxyphenyl)ethanol (**10b**).

In order to clarify the reaction mechanism and structural features affecting the transformation of 3,4-dihydroisocoumarins to 1-hydroxyisochromans by reduction with lithium aluminum hydride, 8-hydroxy-3-phenyl-3,4-dihydroisocoumarin (**11a**) and 8-acetoxy-3-phenyl-3,4-dihydroisocoumarin (**11b**), which are 3,4-dihydroisocoumarins lacking substituents in the $C_{(3)}$ -phenyl group, and 8-acetoxy-3,4-dihydroisocoumarin (**12b**) were reduced with lithium aluminum hydride. Both **11a** and **11b** gave 1,8-dihydroxy-3-phenylisochroman (**13**), 8-hydroxy-3-phenylisochroman (**14**), and 2-(3-hydroxy-2-hydroxymethyl)-1-phenylethanol (**15**), while **12b** gave a mixture of equal amounts of 1,8-dihydroxyisochroman (**16a**) and 2-formyl-3-hydroxyphenylethanol (**16b**) (Chart 3).

On refluxing 1-hydroxyisochroman prepared according to the method of Rieche and Schmitz⁵⁾ with ethanol for 3.5 hr, 1-ethoxyisochroman (**17**) was obtained in quantitative yield. Heating **10a** with benzyl alcohol or veratryl alcohol gave 1-benzyloxy-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**18**) or 8-hydroxy-1-veratryloxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**19**) respectively (Chart 2).

5) A. Rieche and E. Schmitz, *Chem. Ber.*, **89**, 1254 (1956).

Thus, it became clear that the ethoxyl group at the C_{4b}-position of **5** and **7** had arisen by exchange of the C_{4b}-hydroxyl group of 1,8-dihydroxyisochromans with the ethoxyl group of ethanol during the recrystallization of 1,8-dihydroxyisochromans in the reduction mixture.

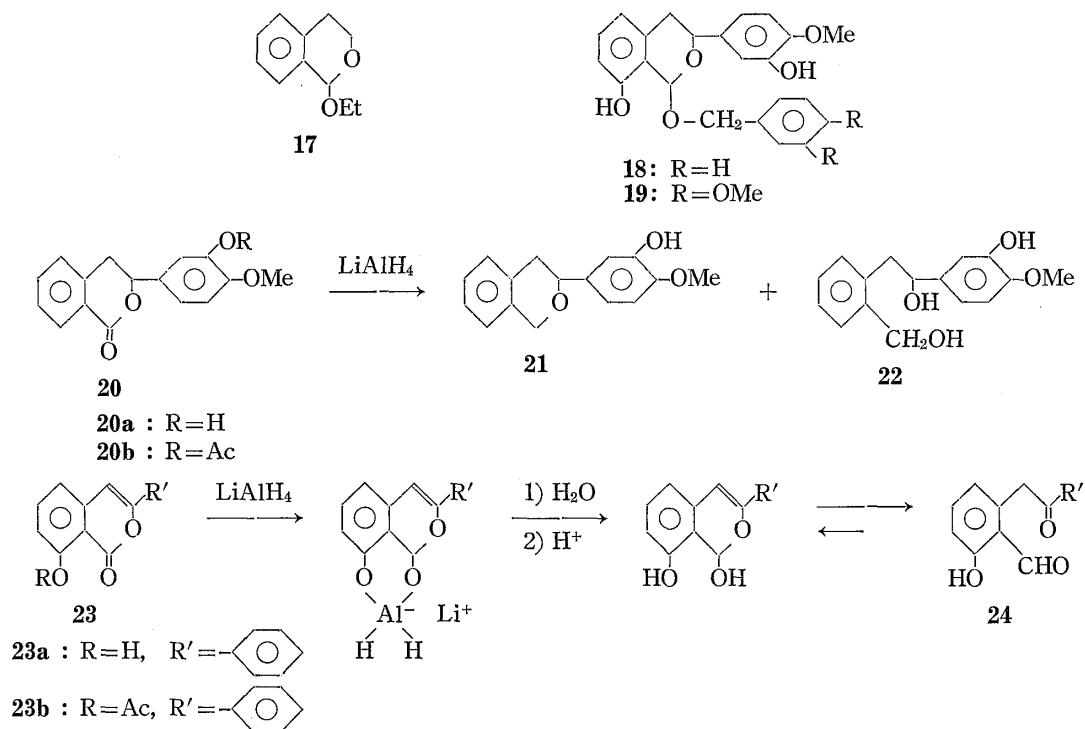


Chart 2

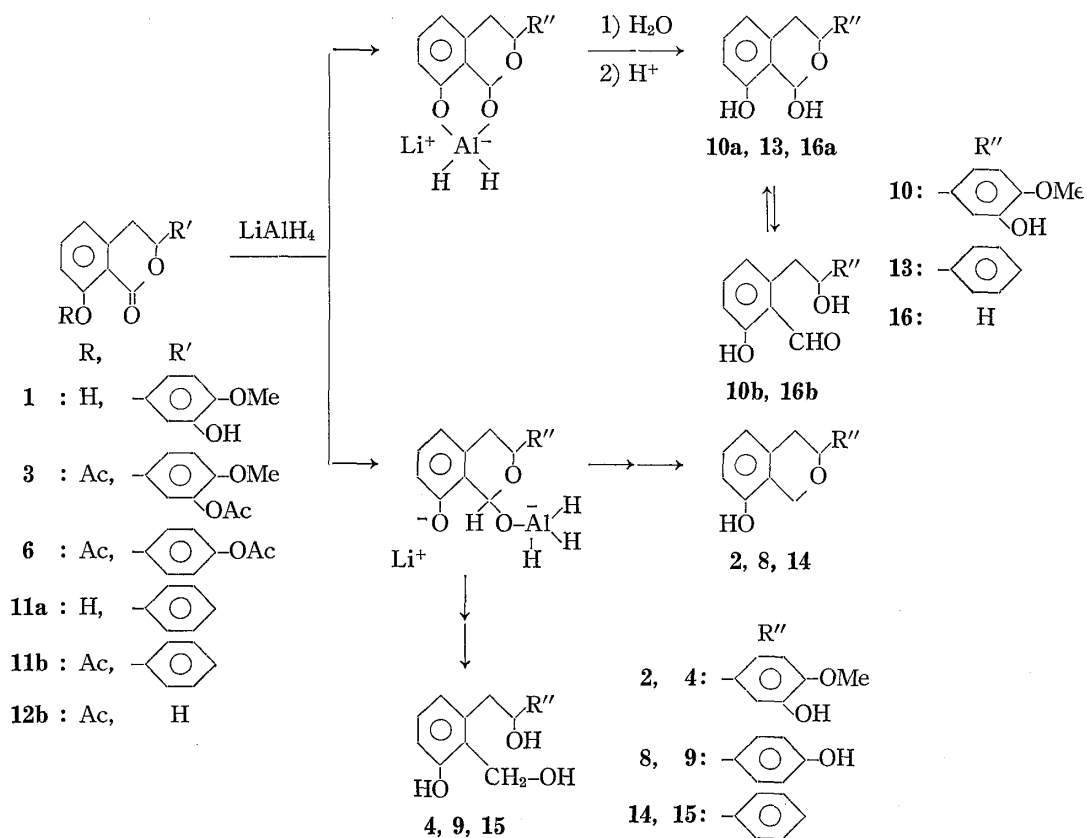


Chart 3

Reduction of 3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydroisocoumarin (**20a**) or 3-(3-acetoxy-4-methoxyphenyl)-3,4-dihydroisocoumarin (**20b**), which are 3,4-dihydroisocoumarins lacking the C₈-hydroxyl or C₈-acetoxy group, gave 3-(3-hydroxy-4-methoxyphenyl)isochroman (**21**) and 1-(3-hydroxy-4-methoxyphenyl)-2-(2-hydroxymethylphenyl)ethanol (**22**), and no 1-hydroxyisochroman derivative was formed (Chart 2).

These results indicate that the presence of either a hydroxyl or an acetoxy group at the C₈-position is essential for the formation of 1-hydroxyisochromans, and a 3- to 5-fold molar excess of lithium aluminum hydride relative to **3** appears to be necessary to obtain a high yield of **10**.

The reduction of isocoumarins was also examined. 8-Hydroxy-3-phenylisocoumarin (**23a**) and 8-acetoxy-3-phenylisocoumarin (**23b**) were reduced with lithium aluminum hydride. Both **23a** and **23b** gave 2-formyl-3-hydroxybenzyl phenyl ketone (**24**), in contrast to the formation of 2-(2-hydroxymethylphenyl)-1-phenylethanols upon reduction of 3-phenylisocoumarins lacking a C₈-hydroxyl or C₈-acetoxy group (Chart 2).

On the basis of these findings, the mechanism of reduction of 8-hydroxy-3,4-dihydroisocoumarins or 8-acetoxy-3,4-dihydroisocoumarins to form 1-hydroxyisochromans and isochromans is proposed to be as shown in Chart 3. 1-Hydroxyisochroman might be stabilized to resist further reduction by the formation of an aluminum-chelating intermediate. If such a chelating intermediate is not formed, isochromans and 2-(2-hydroxymethylphenyl)ethanols may be formed.

In view of these considerations, lithium borohydride was used in place of lithium aluminum hydride for the reduction of **11a**, and **13** was formed only in low yield (1%).

Because of the difference in the yields of 1-hydroxyisochromans (**13**) from **11b** with the two reducing agents, it was considered that the chelate effect of boron was weaker than that of aluminum. Therefore, a magnesium chelate of **11a** was prepared by the addition of methanolic ammonia to a mixture of **11a** and magnesium chloride, and was reduced with lithium aluminum hydride under the same conditions. As a result, **13** was obtained in 50% yield, with 44% recovery of the starting material (**11a**).

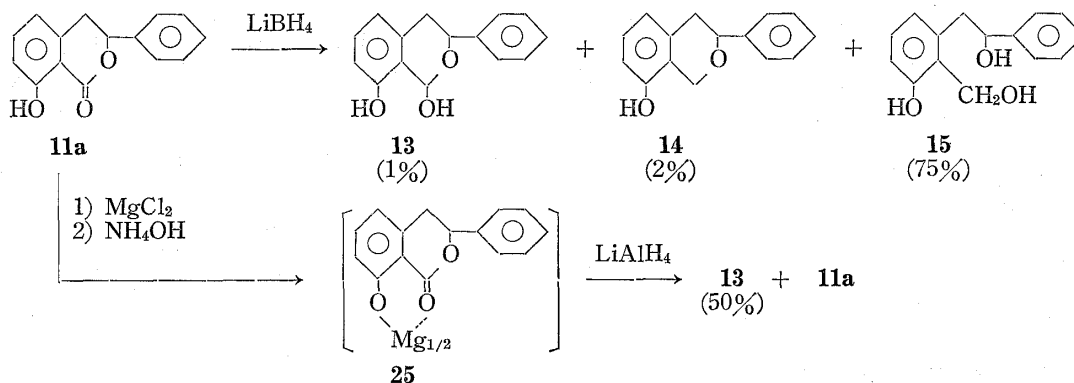


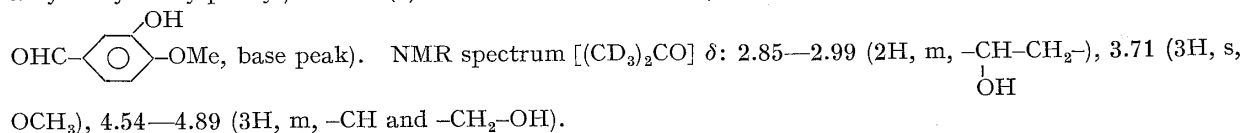
Chart 4

Experimental⁶⁾

Reduction of Diacetylphyllodulcin (3**) with LiAlH_4** —Experimental a) A solution of **3** (3.7 g, 10 mmol) in dry dioxane (100 ml) was added dropwise to a cooled solution of LiAlH_4 (1.9 g, 50 mmol) in dry Et_2O (300

6) All melting points were measured on a micro hot-stage apparatus and are uncorrected. NMR spectra were obtained on a Hitachi R-22 spectrometer at 90 MHz, employing tetramethylsilane as an internal standard. Mass spectra were obtained with a Shimadzu LKB-9000 spectrometer, IR spectra were recorded on a Nihon Bunko A-102 spectrometer, and high-performance liquid chromatography was monitored with a Shimadzu 830 spectrometer.

ml) with stirring. The mixture was stirred for 1 hr at 0–5° and then for further 5 hr at 40–45°. After decomposing excess LiAlH_4 by the addition of H_2O , the mixture was acidified with 5% H_2SO_4 , and extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over MgSO_4 , and the solvent was evaporated off. The resulting residue was refluxed with EtOH and chromatographed on a column of silica gel, eluting with CHCl_3 . The first fraction gave 1.49 g (47%) of 1-ethoxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**5**), which was recrystallized from EtOH , mp 250–251.5°. MS m/e : 316 (M^+), 270 ($\text{M}^+ - \text{EtOH}$, base peak). *Anal.* Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_5$: C, 68.34; H, 6.37. Found: C, 68.31; H, 6.29. NMR spectrum $[(\text{CD}_3)_2\text{CO}]$ δ : 1.18 (3H, t, $J=8$ Hz, OCH_2CH_3), 5.08 (1H, broad t, $J=7$ Hz, $\text{C}_{(3)}\text{H}$), 5.89 (1H, s, $\text{C}_{(4)}\text{H}$). The second fraction gave 8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**2**) (0.21 g, 8%), which was recrystallized from CCl_4 , mp 173–174°. NMR and mass spectra were identical with those of **2** prepared previously.²⁾ The final fraction gave 0.29 g (10%) of 1-(3-hydroxy-4-methoxyphenyl)-2-(3-hydroxy-2-hydroxymethylphenyl)ethanol (**4**) as a viscous oil. MS m/e : 290 (M^+), 272 ($\text{M}^+ - \text{H}_2\text{O}$), 120 ($\text{M}^+ - \text{H}_2\text{O} -$

OCH_3), 4.54–4.89 (3H, m, $-\text{CH}$ and $-\text{CH}_2-\text{OH}$).


Experimental b) A solution of **3** (0.5 g, 1.35 mmol) in dry THF (20 ml) was added dropwise to a cooled solution of LiAlH_4 (0.26 g, 6.84 mmol) in dry THF (5 ml). The mixture was stirred at 0–5° for 1 hr. After decomposing excess LiAlH_4 by the addition of H_2O , the mixture was neutralized with CO_2 , and extracted with AcOEt (free of EtOH). The extract was washed with sat. NaCl solution, dried over MgSO_4 , and the solvent was evaporated off. The resulting residue was chromatographed on silica gel and the column was eluted with CH_2Cl_2 (free of EtOH). The first fraction gave 0.12 g (31%) of a mixture of 1,8-dihydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (**10a**) and 2-(2-formyl-3-hydroxyphenyl)-1-(3-hydroxy-4-methoxyphenyl)ethanol (**10b**). MS m/e : 288 (M^+), 270 ($\text{M}^+ - \text{H}_2\text{O}$, base peak). NMR spectrum $[(\text{CD}_3)_2\text{CO}]$ δ : 5.56 (1H, s, $\text{C}_{(4)}\text{H}$), 10.20 (0.5H, s, formyl proton). The second fraction gave 0.02 g (5.4%) of **2**. NMR and mass spectra were identical with those of **2** prepared previously. The final fraction gave 0.03 g (7.6%) of **4**. NMR and mass spectra were identical with those of **4** prepared previously.

Reduction of Diacetylhydrangenol (6) with LiAlH_4 —A cooled dry Et_2O (72 ml) solution of LiAlH_4 (1.8 g, 4.7 mmol) was treated dropwise with a solution of **6** (1.8 g, 5 mmol) in dry dioxane (72 ml) with stirring. The mixture was stirred for 1 hr at 0–5° and then for a further 5 hr at 40–45°. Excess LiAlH_4 was decomposed by the addition of H_2O . The mixture was acidified with 5% H_2SO_4 , and extracted with AcOEt . The solvent was evaporated off. The resulting residue was refluxed with EtOH , and chromatographed on a column of silica gel, eluting with CHCl_3 . The first fraction gave 0.2 g (13%) of 1-ethoxy-3-(4-hydroxyphenyl)-8-hydroxyisochroman (**7**). Recrystallization from EtOH gave colorless needles, mp 185–186°. MS m/e : 286 (M^+), 240 ($\text{M}^+ - \text{EtOH}$, base peak). *Anal.* Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$: C, 71.31; H, 6.34. Found: C, 71.29; H, 6.31. NMR spectrum $[(\text{CD}_3)_2\text{CO}]$ δ : 1.22 (2H, t, $J=7.9$ Hz, OCH_2CH_3), 2.90 (2H, d, $J=8$ Hz, $\text{C}_{(4)}\text{H}_2$), 3.85 (2H, q, $J=7.9$ Hz, OCH_2CH_3), 5.15 (1H, t, $J=8$ Hz, $\text{C}_{(3)}\text{H}$), 5.92 (1H, s, $\text{C}_{(1)}\text{H}$). The second fraction gave 0.3 g (25%) of 3-(4-hydroxyphenyl)-8-hydroxyisochroman (**8**). Recrystallization from CHCl_3 gave colorless needles, mp 183–184°. MS m/e : 242 (M^+), 119 ($\text{M}^+ - \text{HO}-\text{C}_6\text{H}_4-\text{CHO}$, base peak). *Anal.* Calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$: C, 74.36; H, 5.83. Found: C, 74.31; H, 5.80. NMR spectrum $[(\text{CD}_3)_2\text{CO}]$ δ : 2.88 (2H, d, $J=7$ Hz, $\text{C}_{(4)}\text{H}_2$), 4.60 (1H, t, $J=7$ Hz, $\text{C}_{(3)}\text{H}$), 4.90 (2H, q of AB type, $J=16$ Hz, $\text{C}_{(1)}\text{H}_2$).

Reduction of 8-Acetoxy-3-phenyl-3,4-dihydroisocoumarin (11b) or 8-Hydroxy-3-phenyl-3,4-dihydroisocoumarin (11a) with LiAlH_4 —1) Synthesis of **11a**: AlCl_3 (20 g) was added to a solution of 3-methoxyhomophthalic anhydride (18.42 g, 95.9 mmol) in 260 ml of thiophene-free benzene. After stirring the mixture at 80° for 4 hr, excess AlCl_3 was decomposed by the addition of H_2O . The mixture was acidified with dil. HCl , and the resulting precipitate was collected by suction, washed with sat. KHCO_3 solution and H_2O , then recrystallized from EtOH to give 13.92 g (57%) of 8-hydroxy-3-phenylisocoumarin (**23a**), mp 160–163°. MS m/e : 238 (M^+ , base peak), 210 ($\text{M}^+ - \text{CO}$). NMR spectrum $[(\text{CD}_3)_2\text{CO}]$ δ : 6.82 (1H, s, $\text{C}_{(4)}\text{H}$).

NaBH_4 (15 g) was added to a solution of 8-hydroxy-3-phenylisocoumarin (**23a**) (13.92 g, 58.4 mmol) in a mixture of 180 ml of 4% NaOH solution and 120 ml of EtOH . After stirring the mixture at 40–45° for 6 hr, excess NaBH_4 was decomposed by the addition of dil. H_2SO_4 . The EtOH was removed *in vacuo*, and the mixture was extracted with AcOEt . The extract was washed with 5% KHCO_3 and sat. NaCl solution, dried over MgSO_4 , and the solvent was evaporated off. The residue was recrystallized from benzene– EtOH (1:1) to give 7.46 g (57%) of **11a**, mp 113–114°. MS m/e : 240 (M^+ , base peak), 222 ($\text{M}^+ - \text{H}_2\text{O}$). *Anal.* Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.99; H, 5.03. Found: C, 74.80; H, 5.02. NMR spectrum (CDCl_3) δ : 2.90–5.47 and 5.59 (1H, d, $J=5$ and 10 Hz, $\text{C}_{(3)}\text{H}$).

2) Synthesis of **11b**: Ac_2O (30 g) was added to a solution of **11a** (7.2 g, 30 mmol) in 20 ml of dry pyridine. The mixture was heated at 70° for 1.5 hr, and poured into ice-water. The resulting precipitate was collected by suction, and recrystallized from EtOH to give 7.7 g (91%) of **11b**, mp 124–125°. MS m/e : 282 (M^+), 240 ($\text{M}^+ - \text{COCH}_3$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_4$: C, 72.33; H, 5.00. Found: C, 72.34; H, 5.00.

NMR spectrum (CDCl_3) δ : 2.33 (3H, s, COCH_3), 3.15 (2H, broad t, $J=4.5$ Hz, $\text{C}_{(4)}\text{H}_2$), 5.46 (1H, broad q, $J=4.5$ Hz, $\text{C}_{(6)}\text{H}$).

3) Reduction of **11a** with LiAlH_4 : A solution of **11a** (1.23 g, 5.13 mmol) in dry THF (10 ml) was added dropwise to a cooled solution of 0.4 g (10.5 mmol) of LiAlH_4 in dry THF (10 ml) with stirring. After stirring the reaction mixture at $0-3^\circ$ for 1 hr, excess LiAlH_4 was decomposed by the addition of H_2O . The mixture was neutralized with CO_2 , and extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2 . The first fraction gave 0.3 g (24%) of 1,8-dihydroxy-3-phenylisochroman (**13**). Recrystallization from benzene-cyclohexane (1:1) gave colorless needles, mp $145-147^\circ$.

MS m/e : 242 (M^+), 224 ($\text{M}^+ - \text{H}_2\text{O}$), 136 ($\text{M}^+ - \text{C}_6\text{H}_5\text{CHO}$, base peak). NMR spectrum (d_6 -DMSO) δ : 2.80 (2H, d, $J=6$ Hz, $\text{C}_{(4)}\text{H}_2$), 5.03 (1H, t, $J=6$ Hz, $\text{C}_{(3)}\text{H}$). 2,4-Dinitrophenylhydrazone, mp $253-256^\circ$. MS m/e : 422 (M^+), 316 ($\text{M}^+ - \text{CH}(\text{OH})\text{C}_6\text{H}_4\text{NO}_2$). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_6$: C, 58.53; H, 4.42; N, 13.65. Found:

C, 58.60; H, 4.49; N, 13.55. The second fraction gave 0.093 g (8%) of 8-hydroxy-3-phenylisochroman (**14**), which was recrystallized from cyclohexane, mp $116-118^\circ$. MS m/e : 226 (M^+), 120 ($\text{M}^+ - \text{C}_6\text{H}_5\text{CHO}$, base peak).

Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{O}_2$: C, 79.62; H, 6.24. Found: C, 79.62; H, 6.26. NMR spectrum [$(\text{CD}_3)_2\text{CO}$] δ : 2.82 (2H, d, $J=8$ Hz, $\text{C}_{(4)}\text{H}_2$), 4.56 (1H, d, $J=8$ Hz, $\text{C}_{(3)}\text{H}$), 4.97 (2H, q of AB type, $J=16$ Hz, $\text{C}_{(1)}\text{H}_2$). The final fraction gave 0.125 g (10%) of 2-(3-hydroxy-2-hydroxymethyl)-1-phenylethanol (**15**). Recrystallization from CHCl_3 gave colorless needles, mp $103.5-104^\circ$. MS m/e : 244 (M^+), 226 ($\text{M}^+ - \text{H}_2\text{O}$), 120 ($\text{M}^+ - \text{H}_2\text{O} - \text{C}_6\text{H}_5\text{CHO}$, base peak). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3$: C, 73.75; H, 6.60. Found: C, 74.05; H, 6.47.

NMR spectrum [$(\text{CD}_3)_2\text{CO}$] δ : 2.92 and 2.97 (2H, d,d, $J=2$ and 5 Hz, $-\text{CH}_2-\text{CH}(\text{OH})-$).

4) Reduction of **11b** with LiAlH_4 : A solution of **11b** (1 g, 3.55 mmol) in dry THF (10 ml) was added dropwise to a cooled solution of LiAlH_4 (0.34 g, 8.94 mmol) in dry THF (10 ml) with stirring. After stirring the reaction mixture at $0-5^\circ$ for 1 hr, excess LiAlH_4 was decomposed by the addition of H_2O . The mixture was neutralized with CO_2 , and extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2 . **13** (20%), **14** (8%), and **15** (9%) were obtained. The NMR and mass spectra were identical with those of authentic samples of **13**, **14**, and **15** obtained previously.

Reduction of 8-Acetoxy-3,4-dihydroisocoumarin (12b) with LiAlH_4 —1) Synthesis of 8-Hydroxy-3,4-dihydroisocoumarin (**12a**): A solution of methyl 2-carboxy-3-hydroxyphenylacetate (4.03 g, 19 mmol) in 120 ml of dry THF was added to a solution of 0.83 g (38 mmol) of LiBH_4 . The solution was clear at first, then gradually became cloudy during heating. After refluxing for 4 hr, most of the solvent was distilled off, and the residue was cooled. H_2O was added dropwise, and the mixture was acidified with dil. H_2SO_4 . The mixture was then extracted with Et_2O , and the extract was washed with Na_2CO_3 and H_2O , dried, and the solvent was evaporated off. The residue was recrystallized from H_2O to give 1.76 g (60%) of 8-hydroxy-3,4-dihydroisocoumarin (**12a**), mp $51-53^\circ$. MS m/e : 164 (M^+). Anal. Calcd for $\text{C}_9\text{H}_8\text{O}_3$: C, 65.85; H, 4.91. Found: C, 65.88; H, 5.00. NMR spectrum [$(\text{CD}_3)_2\text{CO}$] δ : 3.08 (2H, t, $J=6$ Hz, $\text{C}_{(4)}\text{H}_2$), 4.63 (2H, t, $J=6$ Hz, $\text{C}_{(3)}\text{H}_2$).

2) Synthesis of **12b**: Ac_2O (10 g) was added to a mixture of 1.76 g (10.7 mmol) of **12a** in 10 ml of dry pyridine. After stirring the mixture at 70° for 1.5 hr, the mixture was poured into ice-water, and the resulting precipitate was collected by suction, followed by recrystallization from MeOH to give 1.33 g (60%) of **12b**, mp $141-142^\circ$. MS m/e : 206 (M^+), 163 ($\text{M}^+ - \text{CH}_3\text{CO}$). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_4$: C, 64.07; H, 4.89. Found: C, 64.00; H, 4.99. NMR spectrum (CDCl_3) δ : 2.34 (3H, s, CH_3CO), 3.04 (2H, t, $J=7$ Hz, $\text{C}_{(4)}\text{H}_2$), 4.47 (2H, t, $J=7$ Hz, $\text{C}_{(3)}\text{H}_2$).

3) Reduction of **12b** with LiAlH_4 : A solution of **12b** (0.58 g, 2.8 mmol) in dry THF (20 ml) was added to a cooled dry THF solution (10 ml) of LiAlH_4 (0.21 g, 5.5 mmol) dropwise with stirring. The reaction mixture was stirred at $0-3^\circ$ for a further 1 hr. Excess LiAlH_4 was decomposed by the addition of H_2O . The mixture was neutralized with CO_2 , and extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on silica gel and the column was eluted with CH_2Cl_2 . From the eluate, 0.1 g (22%) of a mixture of **16a** and **16b** was obtained, mp $205-208^\circ$. NMR spectrum (CDCl_3) δ : 5.57 (1H, s, $\text{C}_{(1)}\text{H}$), 10.60 (1H, s, chelated aldehyde). 2,4-Dinitrophenylhydrazone, mp $242-244^\circ$. MS m/e : 346 (M^+), 149 ($\text{M}^+ - \text{HNHN}-\text{C}_6\text{H}_3(\text{NO}_2)_2$).

Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_6$: C, 52.02; H, 4.08; N, 16.18. Found: C, 52.35; H, 4.00; N, 16.23.

Reduction of 8-Hydroxy-3-phenylisocoumarin (23a) with LiAlH_4 —A solution of **23a** (0.58 g, 2.43 mmol) in dry THF (10 ml) was added dropwise to a cooled solution of 0.19 g (5 mmol) of LiAlH_4 in dry THF (5 ml) with stirring. The mixture was stirred at 0° for a further 1 hr. Excess LiAlH_4 was decomposed by the addition of H_2O and the mixture was neutralized with CO_2 , then extracted with AcOEt . The extract was

washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2 : 0.43 g (74%) of 3-hydroxy-2-formylbenzyl phenyl ketone (**24**) was obtained, mp 105.5–106°. MS m/e : 240 (M^+), 222 ($\text{M}^+ - \text{H}_2\text{O}$). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.99; H, 5.03. Found: C, 75.19; H, 4.98. NMR spectrum (CDCl_3) δ : 4.54 (2H, s, CH_2CO), 10.00 (1H, s, $\text{C}_{(3)}$ -formyl proton).

Reduction of 8-Acetoxy-3-phenylisocoumarin (23b) with LiAlH_4 —A solution of **23b** (2 g, 7.14 mmol) in dry THF (20 ml) was added dropwise to a cooled solution of 0.54 g (14.2 mmol) of LiAlH_4 in dry THF (5 ml) with stirring. The mixture was stirred at 0–5° for a further 1 hr. Excess LiAlH_4 was decomposed by the addition of H_2O and the mixture was neutralized with CO_2 , then extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on silica gel and the column was eluted with CH_2Cl_2 to give 1.08 g (63%) of **24**. Its NMR and mass spectra were identical with those of **24** obtained previously.

Reduction of Di(8-hydroxy-3-phenyl-3,4-dihydroisocoumarin)-magnesium (II) (25) with LiAlH_4 —1) Synthesis of a Chelate Compound (**25**) of **11a** with Magnesium: A solution of 0.399 g (4.2 mmol) of MgCl_2 and 1 g (4.2 mmol) of **11a** in 20 ml of MeOH was treated with 10% methanolic ammonia with stirring until precipitation was complete. Stirring was continued for a further 1 hr, then the precipitate was collected and washed with MeOH several times to give 0.869 g (83%) of the chelate compound. The mp was higher than 300°. IR $\nu_{\text{max}}^{\text{NaCl}}$ cm^{-1} : 1650 ($\text{C}=\text{O}$).

2) Reduction of **25** with LiAlH_4 : A solution of **25** (0.5 g, 1.99 mmol) in dry THF (20 ml) was added dropwise to a cooled solution of LiAlH_4 (0.073 g, 1.92 mmol) in dry THF (5 ml). After stirring the mixture at 5° for 1 hr, excess LiAlH_4 was decomposed by the addition of H_2O . The mixture was acidified with 5% H_2SO_4 , and extracted with AcOEt . The extract washed with sat. NaCl solution, dried over anhyd. MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2 . The first fraction gave 0.239 g (50%) of **13**. The NMR and mass spectra were identical with those of **13** obtained previously. The second fraction gave 0.2 g (44%) of **11a**.

Reduction of **11a with LiBH_4** —A solution of **11a** (1.5 g, 6.3 mmol) in dry THF (15 ml) was added dropwise to a cooled solution of LiBH_4 (0.33 g, 12.8 mmol) in dry THF (20 ml) with stirring. The reaction mixture was stirred for 1 hr at 5° and then for a further 4 hr at 20–25°. After decomposing excess LiBH_4 by the addition of H_2O , the mixture was neutralized with CO_2 , and extracted with AcOEt . The extract was washed with sat. NaCl solution, dried over MgSO_4 , and the solvent was evaporated off. The residue was chromatographed on a silica gel column, eluting with CH_2Cl_2 , to give 0.99 g (75%) of **15**, 0.014 g (1%) of **13**, and 0.027 g (2%) of **14**. The NMR and mass spectra were identical with those of authentic samples of **13**, **14**, and **15**.

Heating 1,8-Dihydroxy-3-(3-hydroxy-4-methoxyphenyl)isochroman (10) with Benzyl Alcohol and Veratryl Alcohol—1) Synthesis of 1-Benzyloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**18**): A mixture of 0.5 g (1.73 mmol) of **10a** and 0.19 g (1.75 mmol) of benzyl alcohol was heated at 60° for 1 hr. After cooling the mixture, the precipitate was collected by suction and recrystallized from benzene-*n*-hexane (1:3) to give 0.49 g (75%) of 1-benzyloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**18**), mp 86–88°. MS m/e : 378 (M^+), 270 ($\text{M}^+ - \text{HOCH}_2-\text{C}_6\text{H}_5$, base peak). NMR spectrum (CDCl_3) δ : 2.93 (2H, broad t, $J=7$ Hz, $\text{C}_{(4)}\text{H}_2$), 3.88 (3H, s, OCH_3), 4.83 (1H, s, $-\text{OCH}-\text{C}_6\text{H}_5$), 4.89 (1H, s, $-\text{OCH}-\text{C}_6\text{H}_5$), 5.04 (1H, broad t, $J=7$ Hz, $\text{C}_{(3)}\text{H}$), 5.91 (1H, s, $\text{C}_{(1)}\text{H}$). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{O}_5$: C, 73.00; H, 5.86. Found: C, 73.30; H, 6.19.

2) Synthesis of 1-Veratryloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**19**): Compound **10a** (0.4 g, 1.38 mmol) was heated with 0.24 g (1.42 mmol) of veratryl alcohol at 60° for 1 hr. After cooling the mixture, the precipitate was collected by suction and recrystallized from benzene-cyclohexane (1:3) to give 0.468 g (77%) of 1-veratryloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**19**), mp 242–243°. MS m/e : 438 (M^+), 270 ($\text{M}^+ - \text{HOCH}_2-\text{C}_6\text{H}_2(\text{OMe})_2$, base peak). Anal. Calcd for $\text{C}_{25}\text{H}_{26}\text{O}_7$: C, 68.48; H, 5.98. Found: C, 68.50; H, 5.91. NMR spectrum (CDCl_3) δ : 2.88 (2H, broad t, $J=7$ Hz, $\text{C}_{(4)}\text{H}_2$), 4.73 (1H, s, $-\text{OCH}-\text{C}_6\text{H}_2(\text{OMe})_2$), 4.77 (1H, s, $-\text{OCH}-\text{C}_6\text{H}_2(\text{OMe})_2$), 4.93 (1H, broad t, $J=7$ Hz, $\text{C}_{(3)}\text{H}$), 5.90 (1H, s, $\text{C}_{(1)}\text{H}$).