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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 $C_{(8)}$-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 $C_{(8)}$-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 study[2] 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.

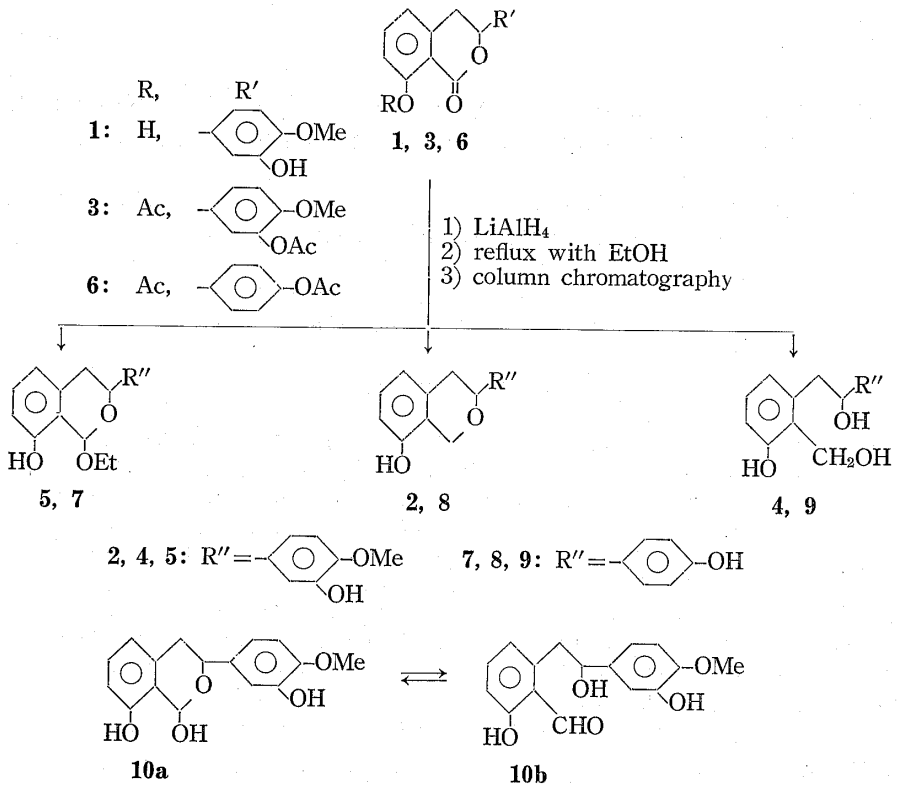


Chart 1

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 Schmitz[5] 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 $C_{(1)}$-position of **5** and **7** had arisen by exchange of the $C_{(1)}$-hydroxyl group of 1,8-dihydroxyisochromans with the ethoxyl group of ethanol during the recrystallization of 1,8-dihydroxyisochromans in the reduction mixture.

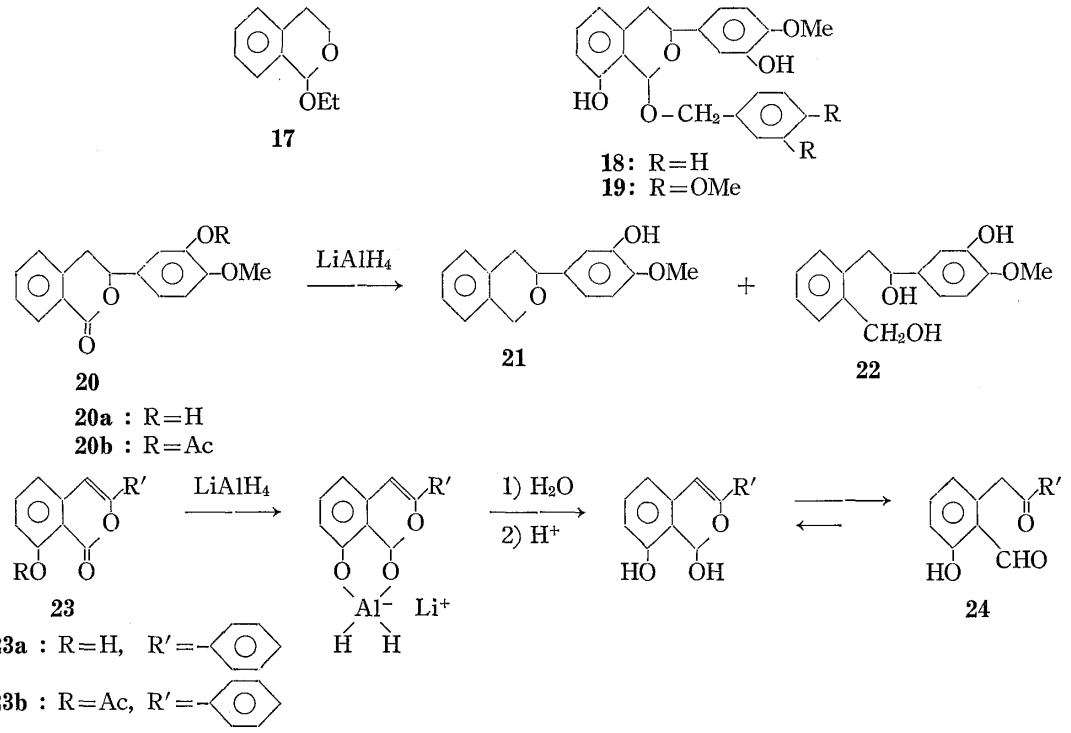


Chart 2

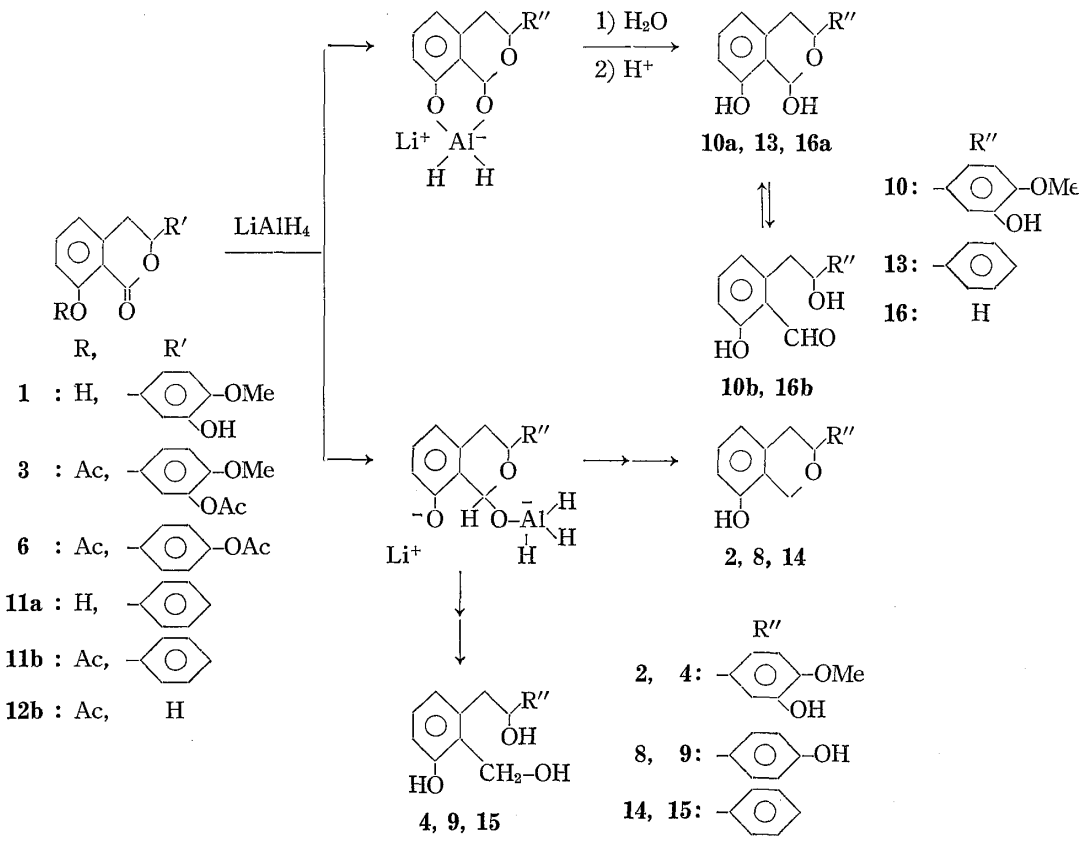


Chart 3

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 $C_{(8)}$-hydroxyl or $C_{(8)}$-acetoxyl 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 acetoxyl group at the $C_{(8)}$-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 $C_{(8)}$-hydroxyl or $C_{(8)}$-acetoxyl 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**).

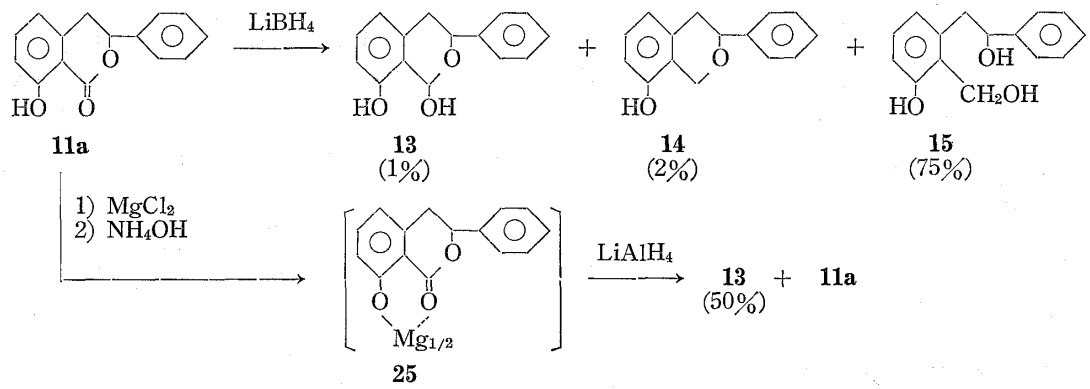
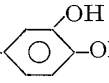


Chart 4

Experimental[6]

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 (M^+-EtOH, base peak). *Anal.* Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.31; H, 6.29. NMR spectrum [$(CD_3)_2CO$] δ: 1.18 (3H, t, $J=8$ Hz, OCH_2CH_3), 5.08 (1H, broad t, $J=7$ Hz, $C_{(3)}H$), 5.89 (1H, s, $C_{(1)}H$). 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 (M^+-H_2O), 120 (M^+-H_2O- OHC–  –OMe, base peak). NMR spectrum [$(CD_3)_2CO$] δ: 2.85—2.99 (2H, m, –CH(OH)–CH_2–), 3.71 (3H, s, OCH_3), 4.54—4.89 (3H, m, –CH(OH) and –CH_2–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 (M^+-H_2O, base peak). NMR spectrum [$(CD_3)_2CO$] δ: 5.56 (1H, s, $C_{(1)}H$), 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.

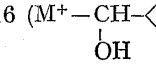
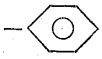
Reduction of Diacetylhydrangenol (6) with $LiAlH_4$——A cooled dry Et_2O (72 ml) solution of $LiAlH_4$ (1.8 g, 4.7 mmol) was treated dropwise with a solution of **6** (1.8 g, 5 mmol) in dry dioxane (72 ml) with stirring. The mixture was stirred for 1 hr at 0—5° and then for a further 5 hr at 40—45°. Excess $LiAlH_4$ 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 (M^+-EtOH, base peak). *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.29; H, 6.31. NMR spectrum [$(CD_3)_2CO$] δ: 1.22 (2H, t, $J=7.9$ Hz, OCH_2CH_3), 2.90 (2H, d, $J=8$ Hz, $C_{(4)}H_2$), 3.85 (2H, q, $J=7.9$ Hz, OCH_2CH_3), 5.15 (1H, t, $J=8$ Hz, $C_{(3)}H$), 5.92 (1H, s, $C_{(1)}H$). 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 (M^+- HO–  –CHO, base peak). *Anal.* Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.31; H, 5.80. NMR spectrum [$(CD_3)_2CO$] δ: 2.88 (2H, d, $J=7$ Hz, $C_{(4)}H_2$), 4.60 (1H, t, $J=7$ Hz, $C_{(3)}H$), 4.90 (2H, q of AB type, $J=16$ Hz, $C_{(1)}H_2$).

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 (M^+-CO). NMR spectrum [$(CD_3)_2CO$] δ: 6.82 (1H, s, $C_{(4)}H$).

$NaBH_4$ (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 (M^+-H_2O). *Anal.* Calcd for $C_{15}H_{12}O_3$: 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,d, $J=5$ and 10 Hz, $C_{(3)}H$).

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 (M^+-COCH_3). *Anal.* Calcd for $C_{17}H_{14}O_4$: 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, brcad t, J=4.5 Hz, $C_{(4)}H_2$), 5.46 (1H, broad q, J=4.5 Hz, $C_{(3)}H$).

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° 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°. MS m/e: 242 (M^+), 224 (M^+-H_2O), 136 (M^+-  -CHO, base peak). NMR spectrum (d_6-DMSO) δ: 2.80 (2H, d, J=6 Hz, $C_{(4)}H_2$), 5.03 (1H, t, J=6 Hz, $C_{(3)}H$). 2,4-Dinitrophenylhydrazone, mp 253—256°. MS m/e: 422 (M^+), 316 (M^+- ). *Anal.* Calcd for $C_{20}H_{18}N_4O_6$: 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°. MS m/e: 226 (M^+), 120 (M^+-  -CHO, base peak). *Anal.* Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.62; H, 6.26. NMR spectrum [$(CD_3)_2CO$] δ: 2.82 (2H, d, J=8 Hz, $C_{(4)}H_2$), 4.56 (1H, d, J=8 Hz, $C_{(3)}H$), 4.97 (2H, q of AB type, J=16 Hz, $C_{(1)}H_2$). 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°. MS m/e: 244 (M^+), 226 (M^+-H_2O), 120 (M^+-H_2O-  -CHO, base peak). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 74.05; H, 6.47. NMR spectrum [$(CD_3)_2CO$] δ: 2.92 and 2.97 (2H, d,d, J=2 and 5 Hz, $-CH_2-\underset{OH}{C}H-$).

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° 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°. MS m/e: 164 (M^+). *Anal.* Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.88; H, 5.00. NMR spectrum [$(CD_3)_2CO$] δ: 3.08 (2H, t, J=6 Hz, $C_{(4)}H_2$), 4.63 (2H, t, J=6 Hz, $C_{(3)}H_2$).

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°. MS m/e: 206 (M^+), 163 (M^+-CH_3CO). *Anal.* Calcd for $C_{11}H_{10}O_4$: 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, $C_{(4)}H_2$), 4.47 (2H, t, J=7 Hz, $C_{(3)}H_2$).

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° 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°. NMR spectrum ($CDCl_3$) δ: 5.57 (1H, s, $C_{(1)}H$), 10.60 (1H, s, chelated aldehyde). 2,4-Dinitrophenylhydrazone, mp 242—244°. MS m/e: 346 (M^+), 149 (M^+- HNHN-  -NO_2). *Anal.* Calcd for $C_{15}H_{14}N_4O_6$: 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 (M^+-H_2O). *Anal.* Calcd for $C_{15}H_{12}O_3$: 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, $C_{(2)}$-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 ν_{max}^{Nujol} cm^{-1}: 1650 (C=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 (M^+- $HOCH_2$–  , base peak). NMR spectrum ($CDCl_3$) δ: 2.93 (2H, broad t, J=7 Hz, $C_{(4)}H_2$), 3.88 (3H, s, OCH_3), 4.83 (1H, s, –OCH– ), 4.89 (1H, s, –OCH– ), 5.04 (1H, broad t, J=7 Hz, $C_{(3)}H$), 5.91 (1H, s, $C_{(1)}H$). *Anal.* Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 73.30; H, 6.19.

2) Synthesis of 1-Veratoryloxy-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-veratoryloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman (**19**), mp 242—243°. MS *m/e*: 438 (M^+), 270 (M^+- $HOCH_2$–  , base peak). *Anal.* Calcd for $C_{25}H_{26}O_7$: 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, $C_{(4)}H_2$), 4.73 (1H, s, –OCH– ), 4.77 (1H, s, –OCH– ), 4.93 (1H, broad t, J=7 Hz, $C_{(3)}H$), 5.90 (1H, s, $C_{(1)}H$).