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Stereoselective Synthesis of *cis*- and *trans*-3-Amino-4-chromanols

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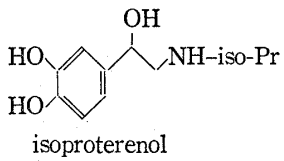
3-Alkylamino-(*cis*-**1a**—**c**) and *trans*-**1a**—**c**), 7-hydroxy-3-isopropylamino-(*cis*-**1d** and *trans*-**1d**), 7,8-dihydroxy-3-isopropylamino-(*cis*-**1e** and *trans*-**1e**) and 6,7-dihydroxy-3-isopropylamino-4-chromanol (*cis*-**1f**) were synthesized. By the use of lithium cyanoborohydride ($LiBH_3CN$), the reductive N-alkylation of 3-amino-4-chromanones with acetone proceeded smoothly to produce 3-isopropylamino-4-chromanones (**12e** and **12f**) in good yields. Stereoselective hydrogenation of 4-chromanones in a basic or an acidic medium to give *trans*- or *cis*-aminoalcohols was discussed on the basis of the thermodynamic stability of the end products. Among the compounds synthesized, 7,8-dihydroxy derivatives showed a strong β_2-stimulating activity, whereas the 6,7-dihydroxy congener was devoid of the activity. The results suggest an important role of the spatial arrangement of functional groups in these catecholamine molecules with regard to their pharmacological properties.

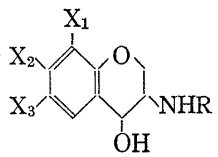
Keywords——catecholamine; chromane; 3-alkylamino-4-chromanol; stereoselective hydrogenation; β-adrenoceptor; β_2-stimulant

During the course of a search for a better bronchodilator, we recently demonstrated that a series of fixed analogs of isoproterenol, 2-amino- and 2-alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols, were strong agonists to the β-adrenoceptor practically devoid of the α-adrenergic-stimulating activity.[2] In this article, the synthesis of some *trans*- and *cis*-3-alkylamino-4-chromanols which bear the structural similarity to 2-alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols is described.

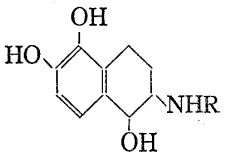
The ethanolamine moiety of β-hydroxyphenethylamine such as isoproterenol has generally been introduced by the coupling reaction of a phenacyl halide and an alkylamine followed by reduction of the carbonyl group. However, 3-halo-4-chromanones undergo cleavage of the pyran ring upon treatment with a strong base.[3,4] We have synthesized 3-amino-4-chromanones by the Neber rearrangement of the corresponding 4-chromanone



isoproterenol



	X_1	X_2	X_3	R
1a :	H	H	H	C_2H_5
1b :	H	H	H	n-C_3H_7
1c :	H	H	H	n-C_4H_9
1d :	H	OH	H	iso-C_3H_7
1e :	OH	OH	H	iso-C_3H_7
1f :	H	OH	OH	iso-C_3H_7



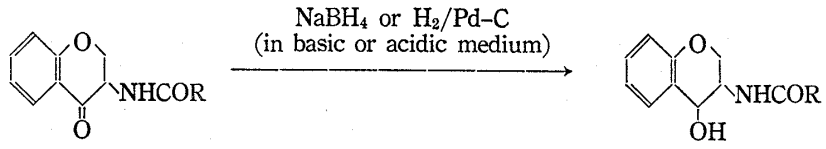
2-alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols

Chart 1

1) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka, 532, Japan.*
2) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
3) P.W. Feit, *Acta Chem. Scand.*, **18**, 2401 (1964).
4) I.M. Lockhart and E.M. Tanner, *J. Chem. Soc.*, **1965**, 3601.

O-(*p*-tolylsulfonyl)oximes or by the reduction of 3-isonitroso-4-chromanones obtained by nitrosation of 4-chromanones.[5-8] N-Alkylation of 3-amino-4-chromanones followed by the stereoselective reduction led to be successively investigated.

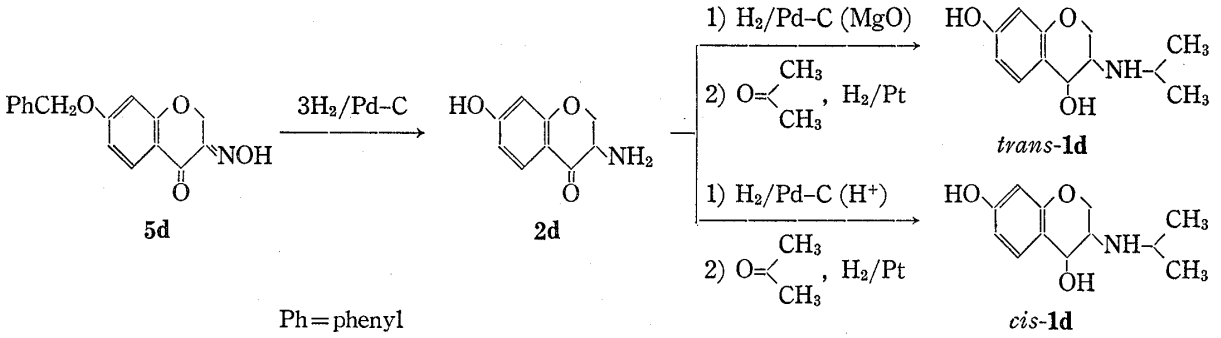
3-Acylamino-4-chromanones(**3a—c**) prepared from 3-amino-4-chromanone hydrochloride (**2a**) by acylation with acid anhydrides were reduced with sodium borohydride in methanol to give *trans*-3-acylamino-4-chromanols (**4a—c**). The lithium aluminum hydride reduction of **4a—c** gave *trans*-3-alkylamino-4-chromanols (*trans*-**1a—c**). Hydrogenation of **3a** in an acidic solution containing hydrochloric acid also gave *trans*-3-acetylamino-4-chromanol. *cis*-3-Alkylamino-4-chromanols (*cis*-**1a—c**) were prepared by alkylation of *cis*-3-amino-4-chromanol[5] with alkyl halides and potassium carbonate in tetrahydrofuran.



3a—3c *trans*-**4a—***trans*-**4c**

Chart 2

7-Benzyloxy-4-chromanone[9] prepared from resorcinol in two steps was nitrosated with isoamyl nitrite and potassium butoxide in *n*-butanol to give 7-benzyloxy-3-isonitroso-4-chromanone (**5d**). Complete hydrogenation of **5d** with 5% palladium charcoal in a basic solution containing magnesium oxide afforded *trans*-3-amino-7-hydroxy-4-chromanol (*trans*-**6d**), which was reductively alkylated with acetone in the presence of platinum-black to give *trans*-7-hydroxy-3-isopropylamino-4-chromanol (*trans*-**1d**). On the other hand, acidic hydrogenation of **5d** and subsequent reductive alkylation afforded *cis*-**1d**. When the hydrogenation was discontinued after the absorption of 3 moles of hydrogen and hydrochloric acid was added to the reaction mixture, 3-amino-7-hydroxy-4-chromanone (**2d**) was isolated as the hydrochloride. Further hydrogenation of **2d** in a basic or acidic medium and subsequent reductive alkylation afforded *trans*-**1d** or *cis*-**1d**, respectively.



5d **2d** *trans*-**1d** *cis*-**1d**

Ph=phenyl

Chart 3

7,8-Dimethoxy-[10] and 6,7-dimethoxy-4-chromanone[11] have been synthesized from 2,3-dimethoxy- and 3,4-dimethoxyphenols, respectively. However, since yields of the condensation reaction of these phenols (**7e, f**) with *β*-chloropionic acid are low (*ca.* 30 %), a practical method for synthesis of *β*-phenoxypropionic acids was investigated. We found

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6) N.V. Dudykina and V.A. Zagorevskii, *J. Org. Chem. USSR*, **2**, 2179 (1966).
7) I. Isaka, K. Kubo, M. Takashima, and M. Murakami, *Yakugaku Zasshi*, **87**, 1556 (1967).
8) D. Huckle, I.M. Lockhart, and M. Wright, *J. Med. Chem.*, **12**, 277 (1969).
9) A.O. Fitton and G.R. Ramage, *J. Chem. Soc.*, **1962**, 4870.
10) P. Pfeiffer, H. Oberlin, and E. Konermann, *Chem. Ber.*, **58**, 1947 (1925).
11) H.F. Birch, A. Robertson, and T.S. Subramanian, *J. Chem. Soc.*, **1936**, 1832.

that sodium 2,3-dimethoxy (**7e**) and 3,4-dimethoxyphenolates (**7f**) reacted readily with β-propiolactone in dimethylformamide (DMF) to give the corresponding β-phenoxypropionic acids (**8e, f**) in fairly good yield. The products (**8e, f**) were cyclized in polyphosphoric acid to 4-chromanones (**9e, f**) which were converted to their oximes (**10e, f**) by the conventional method. 4-Chromanone O-(*p*-tolylsulfonyl)oximes (**11e, f**) were obtained by tosylation of oximes with *p*-toluenesulfonyl chloride in pyridine. The Never rearrangement of **11e, f** with potassium ethoxide in ethanol and subsequent treatment with hydrochloric acid formed 3-amino-4-chromanone hydrochloride (**2e, f**). Compound (**2e**) was demethylated by refluxing with aqueous hydrobromic acid solution to give 3-amino-7,8-dihydroxy-4-chromanone hydrobromide (**13e**) which was hydrogenated in the presence of 5% palladium charcoal and two equivalents of sodium acetate in methanol, followed by reductive alkylation with acetone to give *trans*-7,8-dihydroxy-3-isopropylamino-4-chromanol acetate (*trans*-**1e**). Hydrogenation of **13e** in an acidic solution and subsequent reductive alkylation with acetone failed to give pure *cis*-isomer. 3-Amino-4-chromanones are stable in their salt form, but easily dimerize into dihydropyrazine derivatives as the free base.[7] N-Alkylation of 3-amino-4-chromanones was unsuccessful in usual ways. Lithium cyanoborohydride,[12] a reductive alkylating reagent recently developed,[13,14] was successfully used for this process. Thus, reductive alkylation of **2e** and **2f** with acetone by lithium cyanoborohydride ($LiBH_3CN$) gave 7,8-dimethoxy-(**12e**) and 6,7-dimethoxy-3-isopropylamino-4-chromanone hydrochloride (**12f**), respectively. O-Demethylation of **12e** by refluxing with 47% hydrobromic acid solution

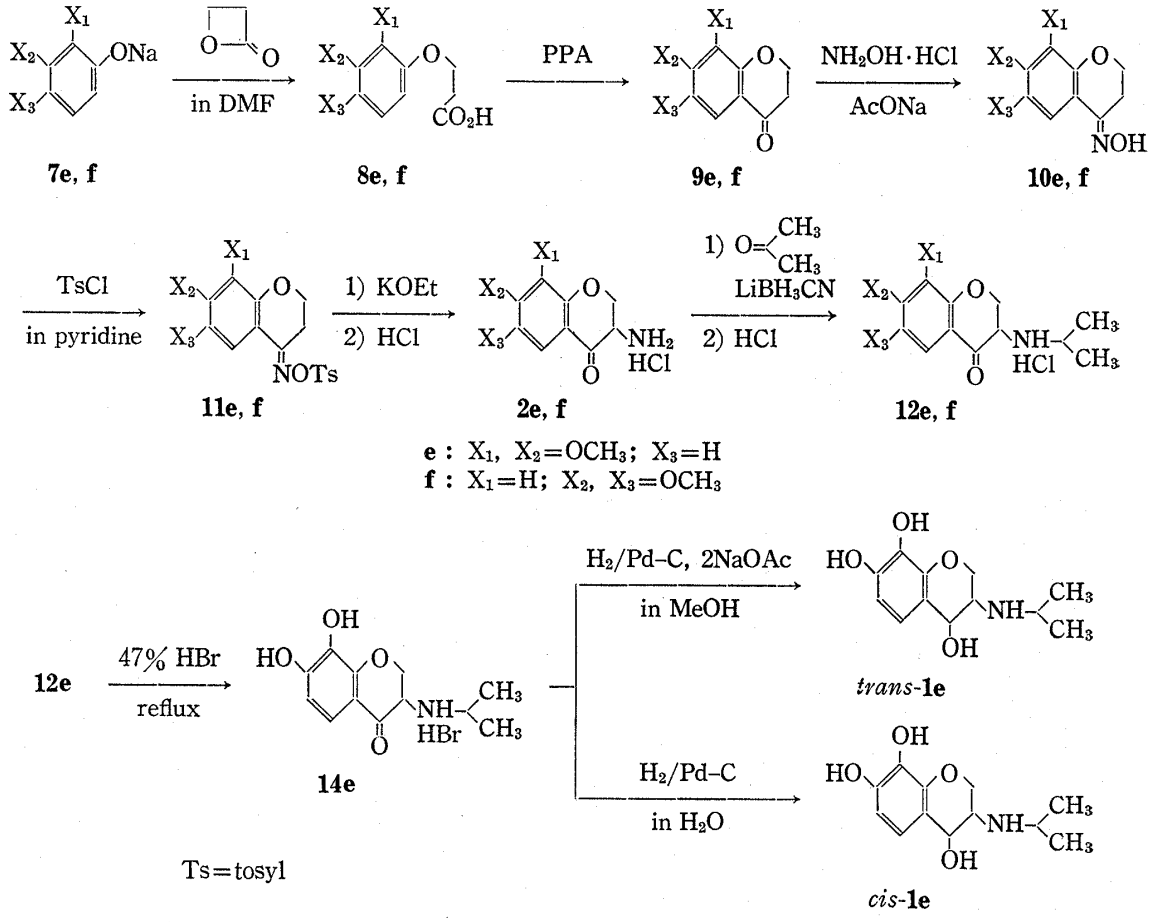


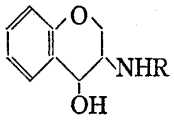
Chart 4

12) G. Wittig, *Ann. Chem.*, **573**, 209 (1951).
13) R.F. Borch and H.D. Durst, *J. Am. Chem. Soc.*, **91**, 3996 (1969).
14) R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

afforded 7,8-dihydroxy-3-isopropylamino-4-chromanone hydrobromide (**14e**). Hydrogenation of **14e** by 5 % palladium charcoal in water and a treatment of the resulting product with sodium acetate gave pure *cis*-**1e** acetate. In the presence of 2 equivalents of sodium acetate, the hydrogenation afforded *trans*-**1e** acetate. Similarly, *cis*-6,7-dihydroxy-3-isopropylamino-4-chromanol hydrobromide (*cis*-**1f** hydrobromide) was obtained from **14f**, but *trans*-isomer was not isolated by the hydrogenation under basic condition.

Above stereoselective hydrogenation of 3-amino- or 3-alkylamino-4-chromanones can be explained by the difference of thermodynamic stability of the reaction products. Everett and Hyne[15] reported that the most thermodynamically stable conformation of ephedrine was of 180° about the angle between the planes of $C_\beta C_\alpha O$ and $NC_\beta C_\alpha$ in the neutral molecule, while would be of 0° in the ephedrium ion owing to the interaction between Me^+NH_2 and OH, which overwhelms the steric repulsion against each other. As *cis*-3-alkylamino-4-chromanols are stronger bases than *trans*-isomers (Table I), the salts of the *cis*-isomer would be thermodynamically more stable compared with those of *trans*-isomers, leading the acidic hydrogenation of the chromanones to *cis* configuration. The fact that the hydrogenation of the same chromanones in a basic medium gave only *trans*-aminoalcohols might be explained by smaller steric hindrance of these isomers in the state of free bases. The experimental evidence that the hydrogenation of 3-acetylamino-4-chromanone, which lacks an ionizable nitrogen, gave *trans*-chromanols independent of the reaction medium supports the above explanation of stereoselective hydrogenation.

Table I. pK_a values of *cis*- and *trans*-3-Alkylamino-4-chromanols in 50% Ethanol Solution



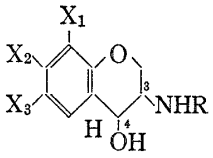
R	pK_a value	
	trans-Isomer	*cis*-Isomer
C_2H_5	7.15	7.65
n-C_3H_7	7.0	7.5
n-C_4H_9	7.1	7.5

The doublets at δ 4.0—5.0 ppm observed in the nuclear magnetic resonance (NMR) spectra of **1a**—**1f** were assigned to C_4–H. The coupling constants ($J_{3,4}$) of *cis*- and *trans*-isomers are found to be 3—4 and 6 Hz, respectively (Table II). It has been reported that the heterocyclic ring of chromans has one of two "sofa conformations",[16,17] in which the dihydropyran ring, except for atom at 2-position, is co-planar with the associated benzene nucleus. In the NMR spectra of 3-alkylamino-4-chromanols, the isomeric hydroxyl group at 4-position showed quasi-axial or quasi-equatorial character. The higher chemical shifts and the larger coupling constants of C_4–H in *trans*-isomers are reasonably attributable to the axial orientation of the C_4–H bond.

The compounds (**1a**—**1f**) were evaluated for their pharmacological activity using tracheal muscle of guinea pig. Detailed pharmacological results will be published elsewhere. 7,8-Dihydroxy-3-isopropylamino-4-chromanols (*cis*-**1e** and *trans*-**1e**) showed significant β_2-stimulatory activity. But 6,7-dihydroxy-3-isopropylamino-4-chromanol (*cis*-**1f**) was inac-

15) D.H. Everett and J.B. Hyne, *J. Chem. Soc.*, **1958**, 1636.
16) E.M. Philbin and T.S. Wheeler, *Proc. Chem. Soc.*, **1958**, 167.
17) B.S. Kirkiacharian and D. Raulais, *Bull. Soc. Chim. France*, **1970**, 1139.

TABLE II. C_4–H Signals of *cis*- and *trans*-3-Alkylamino-4-chromanols



X_1	X_2	X_3	R	Chemical shift, ppm (doublet, $J_{3,4}$, Hz)	
				trans-Isomer	*cis*-Isomer
H	H	H	C_2H_5	4.44[a] (6)	4.62[a] (4)
H	H	H	*n*-C_3H_7	4.44[a] (6)	4.65[a] (4)
H	H	H	*n*-C_4H_9	4.47[a] (6)	4.64[a] (4)
H	OH	H	iso-C_3H_7	4.14[b] (6)	4.20[b] (4)
OH	OH	H	iso-C_3H_7	4.18[c] (6)	4.45[c] (3)
H	OH	OH	iso-C_3H_7	—	4.66[d] (3)

a) free base in $CDCl_3$ solution
b) free base in DMSO-d_6-D_2O solution
c) acetate in DMSO-d_6-D_2O solution
d) hydrobromide in DMSO-d_6-D_2O solution

tive. This result is consistent with that of 2-amino-5,6- and 6,7-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols,[2,18] and may show that the orientation of the ethanolamine moiety and the dihydroxyl group on benzene ring in catecholamine derivatives is important for exhibiting the biological activity.

Experimental[19]

3-Acetylamino-4-chromanone (3a)——**3a** was prepared from **2a** as described by Huckle, *et al.*[8] in 73% yield as colorless needles, mp 108°. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.38; H, 5.25; N, 6.59.

3-Propionylamino-4-chromanone (3b)——To a mixture of **2a** (3.0 g), propionic anhydride (10 ml), AcOEt (60 ml) and H_2O (15 ml) was added in small portions AcONa (8.0 g) at room temperature under stirring. After stirring for a further 7 hr, the organic layer was separated and washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene–petr. ether gave **3b** as colorless needles (2.7 g, 82%), mp 130—131°. IR ν_{max}^{KBr} cm^{-1}: 3350 (NHC=O), 1700 (C=O), 1645 (NHC=O). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.70; H, 6.11; N, 6.37.

3-*n*-Butyrylamino-4-chromanone (3c)——Similarly, **3c** was prepared from **2a** and *n*-butyric anhydride in 75% yield and recrystallized from benzene–hexane to give colorless needles, mp 116°. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.95; H, 6.36; N, 6.03.

***trans*-3-Acetylamino-4-chromanol (4a)**——To a cooled solution of **3a** (2.3 g) in MeOH (20 ml), $NaBH_4$ (130 mg) was added with stirring. After stirring for 1 hr, the reaction mixture was poured into cold H_2O and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Recrystallization from H_2O gave **4a** as colorless needles (1.8 g, 79%), mp 164—166°. IR ν_{max}^{KBr} cm^{-1}: 3270, 1640 (NHC=O). NMR (DMSO-d_6) δ: 4.38 (1H, d, J=6.0 Hz, 4-H). *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.79; H, 6.29; N, 6.67.

18) R.I. Thrift, *J. Chem. Soc.*, **1967**, 288.
19) All melting points were determined with Yanagimoto Micro Melting Point apparatus (microscope hot stage) and are uncorrected. Infrared (IR) spectra were measured with a Hitachi Model 215 infrared spectrophotometer. NMR spectra were determined with a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard.

***trans*-3-Propionylamino-4-chromanol (4b)**——Similarly, **4b** was prepared by $NaBH_4$ reduction of **3b** in 77% yield. Recrystallization from AcOEt gave colorless needles, mp 183—184°. *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.23; H, 6.87; N, 6.35.

***trans*-3-*n*-Butyrylamino-4-chromanol (4c)**——Reduction of **3c** with $NaBH_4$ gave **4c** in 97% yield. Recrystallization from AcOEt afforded colorless needles, mp 156—157°. NMR (DMSO-d_6–D_2O) δ: 4.40 (1H, d, J=6.0 Hz, 4-H). *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.24; H, 7.52; N, 5.98.

***trans*-3-Ethylamino-4-chromanol (*trans*-1a)**——To a solution of **4a** (1.3 g) in dry tetrahydrofuran (THF) (20 ml), was added $LiAlH_4$ (1.0 g). The reaction mixture was refluxed for 2 hr. After decomposition of the excess $LiAlH_4$ with MeOH, the mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Recrystallization from ether–hexane gave *trans*-**1a** as colorless needles (630 mg, 52%), mp 101—102°. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.08; H, 8.18; N, 7.29.

***trans*-3-Propylamino-4-chromanol (*trans*-1b)**——Similarly, *trans*-**1b** was obtained by reduction of **4b** in 65% yield. Recrystallization from ether–petr. ether afforded colorless plates, mp 81—82°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.42; H, 8.31; N, 6.54.

***trans*-3-Butylamino-4-chromanol (*trans*-1c)**——Similarly, *trans*-**1c** was prepared from **4c** in 40% yield. Recrystallization from H_2O–MeOH gave colorless plates, mp 114—115°. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.38; H, 8.58; N, 6.35.

***cis*-3-Ethylamino-4-chromanol (*cis*-1a)**——A mixture of *cis*-3-amino-4-chromanol[5] (1.0 g), EtI (0.6 ml) and K_2CO_3 (500 mg) in THF (8 ml) was stirred for 5 hr at room temperature. The inorganic salt was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica-gel column; elution with benzene–MeOH (3: 1 v/v) gave white crystals. Recrystallization from H_2O–MeOH gave *cis*-**1a** as colorless needles (455 mg, 40%), mp 71—72°. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.57; H, 8.18; N, 7.29.

***cis*-3-Propylamino-4-chromanol (*cis*-1b)**——Similarly, *cis*-**1b** was obtained from *cis*-3-amino-4-chromanol and *n*-PrI in 33% yield. Recrystallization from H_2O–MeOH gave colorless needles, mp 67—68°. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.75; H, 8.61; N, 6.85.

***cis*-3-Butylamino-4-chromanol (*cis*-1c)**——Similarly, *cis*-**1c** was prepared from *cis*-3-amino-4-chromanol and *n*-BuI in 43% yield. Recrystallization from benzene–petr. ether gave colorless needles, mp 78—79°. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.61; H, 8.78; N, 6.44.

7-Benzyloxy-3-isonitroso-4-chromanone (5d)——To a cooled *n*-BuOK–*n*-BuOH solution prepared from metallic potassium (2.4 g) and *n*-BuOH (110 ml) was added 7-benzyloxy-4-chromanone[9] (12.2 g) dissolved in a mixture of anhydrous benzene (20 ml) and anhydrous THF (20 ml). To this, isoamyl nitrite (7.8 g) was then added dropwise at 5—10° with stirring. The reaction mixture was stirred for a further 4 hr and allowed to stand overnight in a refrigerator. The precipitates were collected by filtration, washed with ether and suspended in ice-H_2O (300 ml). The suspension was neutralized with glacial AcOH (6 ml) and the resulting precipitates were collected and washed with H_2O. Recrystallization from benzene–THF gave **5d** as colorless needles (4.6 g, 34%), mp 184—185° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3510, 1680, 1610. *Anal.* Calcd. for $C_{16}H_{13}O_4N$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.59; H, 4.55; N, 4.61.

***trans*-3-Amino-7-hydroxy-4-chromanol (6d)**——A solution of **5d** in a mixture of THF (40 ml), MeOH (10 ml) and H_2O (10 ml) was hydrogenated over Pd-black (500 mg) and MgO (300 mg) at room temperature under atmospheric pressure. After H_2 uptake had ceased (about 10 hr), the reaction mixture was worked up in a usual manner and the crude base was purified by column chromatography on silica-gel using AcOEt: MeOH=3: 1 (v/v) as an eluting solvent. Recrystallization from AcOEt gave *trans*-**6d** as white prisms (234 mg, 18%), mp 164—165°. NMR (DMSO-d_6) δ: 4.08 (1H, d, J=6 Hz, 4-H). *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.68; H, 6.31; N, 7.59.

***trans*-7-Hydroxy-3-isopropylamino-4-chromanol (*trans*-1d)**——A solution of *trans*-**6d** (234 mg) in MeOH (15 ml) and acetone (0.2 ml) was reductively alkylated in the presence of Pt-black (100 mg) and AcONa (82 mg) under H_2 atmosphere at room temperature. After filtration of the catalyst, the filtrate was evaporated to dryness *in vacuo* and the residue was chromatographed on a silica-gel. Elution with AcOEt–benzene (4: 1 v/v) gave *trans*-**1d** as white crystals (128 mg, 52%), mp 82—84°. *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.87; H, 8.04; N, 6.27.

***cis*-7-Hydroxy-3-isopropylamino-4-chromanol (*cis*-1d)**——A solution of **5d** (555 mg) in EtOH (50 ml) and 0.1N HCl (2 ml) was hydrogenated over 5% Pd-carbon (500 mg) at room temperature until H_2 uptake ceased (290 ml, 10 hr). After filtration of the catalyst, the filtrate was evaporated *in vacuo*. The residue composed of *cis*-**6d** and a small amount of *trans*-**6d** was reductively alkylated with acetone (0.4 ml) in MeOH (30 ml) in the presence of Pt-black (10 mg) and AcONa (100 mg) under H_2 atmosphere. The reaction product was worked up as usual and the crude amine obtained was chromatographed on silica-gel using AcOEt–MeOH (2: 1 v/v) as the eluting solvent. Recrystallization from AcOEt–ether gave *cis*-**1d** as white crystals (148 mg), mp 140—142°. *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.75; H, 7.93; N, 6.00.

3-Amino-7-hydroxy-4-chromanone Hydrochloride (2d)——A suspension of **5d** (1.0 g) in MeOH (100 ml) was hydrogenated over Pd-black (50 mg) at room temperature until 3 moles of H_2 had been absorbed, and

then to the reaction mixture was added ethanolic HCl. The reaction mixture was filtered off and the filtrate was evaporated *in vacuo*. The residue was recrystallized from MeOH, giving **2d** as colorless needles (450 mg, 59%), mp 245—246° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1670, 1600. NMR (DMSO-d_6) δ: 4.2—4.6 (2H, m), 4.74 (1H, d, J=5 Hz), 6.35 (1H, d, J=2 Hz, 8-H), 6.55 (1H, d, d, J=9, 2 Hz, 6-H), 7.61 (1H, d, J=9 Hz, 5-H). *Anal.* Calcd. for $C_9H_9O_3N\cdot HCl$: C, 50.12; H, 4.67; N, 6.49. Found: C, 49.98; H, 4.35; N, 6.09.

β-2,3-Dimethoxyphenoxypropionic Acid (8e)——To a suspension of sodium 2,3-dimethoxyphenolate (50 g) in DMF (500 ml), β-propiolactone (35 g) was added at once with ice-cooling and the mixture was stirred vigorously for 2 hr at 55—65°. The reaction mixture was poured into ice-H_2O, acidified with dil. HCl and extracted with ether. After being washed with H_2O, the organic layer was reextracted with 5% $NaHCO_3$ solution. The aqueous solution was washed with ether and neutralized with dil. HCl and the precipitates were collected by filtration. Recrystallization from 80% EtOH gave **8e** as colorless needles (39 g, 53%), mp 102° (lit.[10] mp 101°). *Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.15; H, 6.62.

β-3,4-Dimethoxyphenoxypropionic Acid (8f)——On treatment of sodium 3,4-dimethoxyphenolate with β-propiolactone in DMF as described for **8e**, **8f** was obtained in 59% yield. Recrystallization from 80% EtOH gave colorless needles, mp 136° (lit.[11] mp 136—137°). *Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.21; H, 6.51.

7,8-Dimethoxy-4-chromanone (9e)——A suspension of **8e** (6.3 g) in PPA (70 g) was heated at 60° for 1 hr and the reaction mixture was poured into ice-H_2O and extracted with ether. The organic layer was washed with H_2O and H_2O–$NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. Recrystallization from H_2O gave **9e** as colorless needles (5.1 g, 88%), mp 100° (lit.[10] mp 101°). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.32; H, 6.01.

6,7-Dimethoxy-4-chromanone (9f)——On heating **8f** in PPA at 60° for 1 hr, **9f** was obtained in 87% yield. Recrystallization from H_2O gave colorless needles, mp 123° (lit.[11] mp 123—124°). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.15; H, 6.28.

7,8-Dimethoxy-4-chromanone Oxime (10e)——A mixture of **9e** (5.6 g), $NH_2OH\cdot HCl$ (8 g) and AcONa (8 g) in EtOH (50 ml) was refluxed for 6 hr with stirring and poured into H_2O. The precipitates were collected by filtration and recrystallized from MeOH to give colorless needles of **10e** (5.5 g, 92%), mp 155° (lit.[10] mp 153—154°). *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.25; H, 5.79; N, 6.31.

6,7-Dimethoxy-4-chromanone Oxime (10f)——Treatment of **9f** with $NH_2OH\cdot HCl$ and AcONa gave **10f** in 86% yield. Colorless prisms (from EtOH), mp 183—184°. *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.20; H, 5.96; N, 6.03.

7,8-Dimethoxy-4-chromanone O-(*p*-Tolylsulfonyl)oxime (11e)——To a cooled solution of **10e** (14.8 g) in anhyd. pyridine (60 ml), was added *p*-toluenesulfonyl chloride (14 g) in small portions. The reaction mixture was stirred for 2 hr at 0—5° and poured into ice-H_2O after being left to stand overnight in a refrigerator. The precipitates were collected by filtration, washed with H_2O and cold MeOH successively, and dried to give **11e** as white crystals (23 g, 97%), mp 128—129°. *Anal.* Calcd. for $C_{18}H_{19}O_6NS$: C, 57.28; H, 5.07; N, 3.71. Found: C, 57.08; H, 5.00; N, 3.68.

6,7-Dimethoxy-4-chromanone O-(*p*-Tolylsulfonyl)oxime (11f)——Similarly **11f** was prepared from **10f** and *p*-toluenesulfonyl chloride in 98% yield as white crystals, mp 158—159°. *Anal.* Calcd. for $C_{18}H_{19}O_6NS$: C, 57.28; H, 5.07; N, 3.71. Found: C, 57.31; H, 5.12; N, 3.60.

3-Amino-7,8-dimethoxy-4-chromanone Hydrochloride (2e)——To a cooled ethanolic solution of EtOK prepared from metallic potassium (1.0 g) and anhyd. EtOH (20 ml), a solution of **11e** (7.5 g) in anhyd. benzene (25 ml) was added dropwise at 0—3° under stirring. The reaction mixture was further stirred at 0—3° for 4 hr and after being left to stand overnight in a refrigerator the insoluble material was filtered off. 10% HCl was added to the filtrate with vigorous stirring. After 30 min, the aqueous layer was separated off. The organic layer was extracted 3 times with 10% HCl. The acidic aqueous extracts were combined, washed with benzene and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give **2e** as colorless plates (3.2 g, 61%), mp 204—206° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3400, 1690. NMR (DMSO-d_6) δ: 3.72 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.3—4.7 (2H, m, 2-H), 6.88 (1H, d, J=9 Hz, 6-H), 7.56 (1H, d, J=9 Hz, 5-H). *Anal.* Calcd. for $C_{11}H_{13}O_4N\cdot HCl\cdot 1/3H_2O$: C, 49.73; H, 5.56; N, 5.27. Found: C, 49.76; H, 5.57; N, 5.20.

3-Amino-6,7-dimethoxy-4-chromanone Hydrochloride (2f)——Neber rearrangement of **11f** as described for **2e** afforded **2f** in 85% yield. Colorless needles (from EtOH), mp 237° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3500—3400, 1665. NMR (DMSO-d_6) δ: 3.90 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.70 (1H, s, 8-H), 7.29 (1H, s, 5-H). *Anal.* Calcd. for $C_{11}H_{13}O_4N\cdot HCl\cdot H_2O$: C, 47.57; H, 5.81; N, 5.04. Found: C, 47.31; H, 5.63; N, 4.93.

3-Amino-7,8-dihydroxy-4-chromanone Hydrobromide (13e)——A solution of **2e** (1.8 g) in 47% HBr (10 ml) was refluxed for 2 hr. After cooling, the precipitates were collected by filtration and recrystallized from 80% EtOH to give **13e** as colorless needles (1.2 g, 63%), mp 255° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). NMR (DMSO-d_6) δ: 4.2—4.6 (2H, m, 2-H), 4.67 (1H, d, d, J=7, 3 Hz, 3-H), 6.56 (1H, d, J=9 Hz, 6-H), 7.16 (1H, d, J=9 Hz, 5-H). *Anal.* Calcd. for $C_9H_9O_4N\cdot HBr\cdot H_2O$: C, 36.75; H, 4.11; N, 4.76. Found: C, 36.75; H, 4.02; N, 4.59.

7,8-Dimethoxy-3-isopropylamino-4-chromanone Hydrochloride (12e)——To a cooled solution of **2e** (260 mg) in a mixture of acetone (4 ml) and MeOH (8 ml), $LiBH_3CN\cdot$dioxane (200 mg) was added in small portions

with stirring under N_2 atmosphere. After stirring for further 1 hr at 0—5°, saturated HCl–EtOH (2 ml) was added to the solution. The solvent was then evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH (charcoal) to give **12e** as colorless prisms (203 mg, 68%), mp 187—189° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (DMSO-d_6) δ: 1.29, 1.32 (6H, d, J=6 Hz, $C(CH_3)_2$), 3.70 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.85 (1H, d, J=9 Hz, 6-H), 7.75 (1H, d, J=9 Hz, 5-H). *Anal.* Calcd. for $C_{14}H_{19}O_4N \cdot HCl$: C, 55.72; H, 6.68; N, 4.64. Found: C, 55.51; H, 6.68; N, 4.75.

6,7-Dimethoxy-3-isopropylamino-4-chromanone Hydrochloride (12f)——In the same manner, **12f** was obtained in 70% yield from **2f**, and acetone by the reduction using $LiBH_3CN$·dioxane, as colorless needles (from EtOH–acetone), mp 192—193° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (DMSO-d_6) δ: 1.34, 1.36 (6H, d, J=8 Hz, $C(CH_3)_2$), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.66 (1H, s, 8-H), 7.13 (1H, s, 5-H). *Anal.* Calcd. for $C_{14}H_{19}O_4N \cdot HCl \cdot 1/2H_2O$: C, 54.11; H, 6.81; N, 4.51. Found: C, 53.97; H, 6.64; N, 4.37.

7,8-Dihydroxy-3-isopropylamino-4-chromanone Hydrobromide (14e)——A solution of **12e** (210 mg) in 47% HBr (6 ml) was refluxed for 2 hr and evaporated *in vacuo*. The residue was recrystallized from EtOH (charcoal) to give **14e** as colorless prisms (164 mg, 74%), mp 226—228° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (DMSO-d_6) δ: 1.31, 1.34 (6H, d, J=7 Hz, $C(CH_3)_2$), 6.60 (1H, d, J=8 Hz, 6-H), 7.20 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd. for $C_{12}H_{15}O_4N \cdot HBr$: C, 45.29; H, 5.07; N, 4.40. Found: C, 44.97; H, 5.48; N, 4.10.

6,7-Dihydroxy-3-isopropylamino-4-chromanone Hydrobromide (14f)——A solution of **2f** (1.1 g) in 47% HBr (20 ml) was refluxed for 4 hr and evaporated *in vacuo*. The residue was recrystallized from EtOH (charcoal) to give colorless prisms (680 mg, 60%), mp 230—232° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR (DMSO-d_6) δ: 1.30, 1.32 (6H, d, J=8 Hz, $C(CH_3)_2$), 6.39 (1H, s, 8-H), 7.09 (1H, s, 5-H). *Anal.* Calcd. for $C_{12}H_{15}O_4N \cdot HBr$: C, 45.29; H, 5.07; N, 4.40. Found: C, 45.45; H, 4.98; N, 4.10.

***trans*-7,8-Dihydroxy-3-isopropylamino-4-chromanol Acetate (*trans*-1e)**——A solution of **13e** (800 mg) in MeOH (40 ml) was hydrogenated in the presence of 5% Pd-C (1.0 g) and AcONa (450 mg) under atmospheric pressure at room temperature for 24 hr. After filtration of the catalyst, Pt-black (100 mg) and acetone were added to the filtrate and reductive alkylation was carried out under atmospheric pressure at room temperature for 5 hr. The reaction mixture was filtered off and the filtrate was evaporated *in vacuo* below 30°. The residue was dissolved in THF (30 ml) and the solution was filtered in a N_2 atmosphere. The filtrate was concentrated to *ca.* 5 ml, and after addition of AcOEt, left in a refrigerator to give white crystals (362 mg, 45%), mp 115—117° (decomp.). NMR (DMSO-d_6) δ: 0.99 (6H, d, J=6 Hz, $C(CH_3)_2$), 1.88 (3H, s, CH_3COO), 2.7—3.1 (2H, m), 3.7—4.1 (2H, m), 4.18 (1H, d, J=6 Hz, 4-H), 6.29 (1H, d, J=8 Hz, 6-H), 6.55 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd. for $C_{12}H_{17}O_4N \cdot C_2H_4O_2$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.10; H, 7.17; N, 4.37. Hydrogenation of **14e** in the presence of AcONa using 5% Pd-C as a catalyst gave *trans*-**1e** in 76% yield as an acetate.

***cis*-7,8-Dihydroxy-3-isopropylamino-4-chromanol Acetate (*cis*-1e)**——A solution of **14e** (200 mg) in H_2O (25 ml) was hydrogenated in the presence of 5% Pd-C (200 mg) under atmospheric pressure at room temperature. The uptake of H_2 ceased in 3 hr. The reaction mixture was filtered off in a stream of N_2 and the filtrate was lyophilized. The HBr salt of the *cis*-**1e** obtained was dissolved in MeOH (5 ml) and treated with AcONa (82 mg) in a stream of N_2. The MeOH solution was evaporated *in vacuo* below 30°, and THF (20 ml) was added to the residue. After filtration, the filtrate was evaporated *in vacuo* below 30°. The residue was recrystallized from THF–AcOEt to give white crystals (113 mg, 57%), mp 83—84°. NMR (DMSO-d_6) δ: 1.04, 1.06 (6H, d, J=8 Hz, $C(CH_3)_2$), 1.91 (3H, s, CH_3COO), 2.8—3.2 (2H, m), 3.6—4.1 (3H, m), 4.45 (1H, d, J=3 Hz, 4-H), 6.32 (1H, d, J=8 Hz, 6-H), 6.53 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd. for $C_{12}H_{17}O_4N \cdot C_2H_4O_2$: C, 56.17; H, 7.07; N, 4.68. Found: C, 55.94; H, 7.08; N, 4.34.

***cis*-6,7-Dihydroxy-3-isopropylamino-4-chromanol Hydrobromide (*cis*-1f)**——A solution of **14f** (250 mg) in H_2O (8 ml) was hydrogenated in the presence of 5% Pd-C (300 mg) under atmospheric pressure at room temperature for 40 min. The reaction mixture was filtered in a stream of N_2 and the filtrate was lyophilized to give white powder (235 mg, 84%), which was unstable and hygroscopic in air. NMR (DMSO-d_6) δ: 1.31 (6H, d, J=6 Hz, $C(CH_3)_2$), 4.66 (1H, d, J=3 Hz, 4-H), 6.23 (1H, s, 8-H), 6.68 (1H, s, 5-H). *Anal.* Calcd. for $C_{12}H_{17}O_4N \cdot HBr \cdot 2H_2O$: C, 40.46; H, 6.22; N, 3.93. Found: C, 40.46; H, 5.55; N, 3.72.

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