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Syntheses of conformationally Rigid Catecholamine Derivatives

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2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1**), 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol (**2**) and 5,6-dihydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (**3**), which are conformationally rigid derivatives of noradrenaline, adrenaline and isoproterenol respectively, were synthesized from 2-amino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (**15**) prepared by several modifications of the known procedures. The reduction of 1-carbonyl group into hydroxy group at the final step of the syntheses showed unsatisfactory stereoselectivity affording mixtures of 1,2-*cis* and 1,2-*trans* derivatives. Each *cis* and *trans* isomer of **2** (**2**-*cis* and **2**-*trans*) was obtained by a sequence of reactions employing 5,6-dibenzyloxy materials *via cis*- and *trans*-2-(N-benzyl-N-methylamino)-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (**26**-*cis* and **26**-*trans*).

Keywords——catecholamine; tetrahydronaphthalene; tetrahydronaphthylamine; β-adrenoceptor; β_2-adrenergic activity; rigid catecholamine derivative

In the preceding report,[2] we described the potent β-adrenergic activities of 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1**), 5,6-dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol (**2**) and 5,6-dihydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (**3**), conformationally rigid derivatives of noradrenaline, adrenaline and isoproterenol, respectively. The present paper deals with the details of the chemical syntheses of compounds **1**, **2**, and **3**.

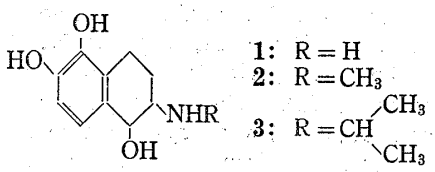

Chart 1

As the common key intermediate in the syntheses of these compounds was employed 2-amino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (**15**), which was prepared by the following modifications of the known procedures.[3,4] 2,3-Dimethoxyphenylacetaldehyde (**6**) was obtained from 2,3-dimethoxybenzaldehyde by Darzens condensation with methyl chloroacetate *via* a glycidic ester derivative (**4**) and its sodium carboxylate (**5**). Knoevenagel condensation of **6** to give 4-(2,3-dimethoxyphenyl)-2-butenoic acid (**7**) followed by catalytic reduction afforded 4-(2,3-dimethoxyphenyl)butanoic acid (**8**). Compound **8** was also obtained from **6** *via* an alternative route, *i.e.* Wittig reaction of **6** with carbomethoxymethylenetriphenylphosphorane affording methyl 4-(2,3-dimethoxyphenyl)-2-butenoate (**10**), hydrogenation of **10** to saturated ester (**11**), and the subsequent hydrolysis leading to **8**. 5,6-Dimethoxy-3,4-dihydro-1(2H)-naphthalenone (**12**) was prepared by cyclization of **8** with polyphosphoric acid or by Friedel-Crafts cyclization of acid chloride (**9**) obtained by treatment of **8** with phosphorous pentachloride. Although direct nitrosation of **12** to afford α-oximino ketone (**14**) have been reported to result in unsatisfactory yields,[3] it was found that the process was markedly improved by conducting the conversion in two stages by way of α-hydroxymethylene ketone (**13**).

1) Location: *Juso, 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) W.K. Sprenger, J.G. Cannon, B.K. Barman, and A.M. Burkman, *J. Med. Chem.*, **12**, 487 (1969).
4) N.F. Elmore and T.J. King, *J. Chem. Soc.*, **1961**, 4425.

Thus the reaction of **12** with ethyl formate in the presence of sodium methoxide gave **13** in 76.5% yield. Compound **13** was converted to **14** in 83.5% yield by treatment with sodium nitrite. Catalytic reduction of **14** over palladium-charcoal readily afforded **15**.

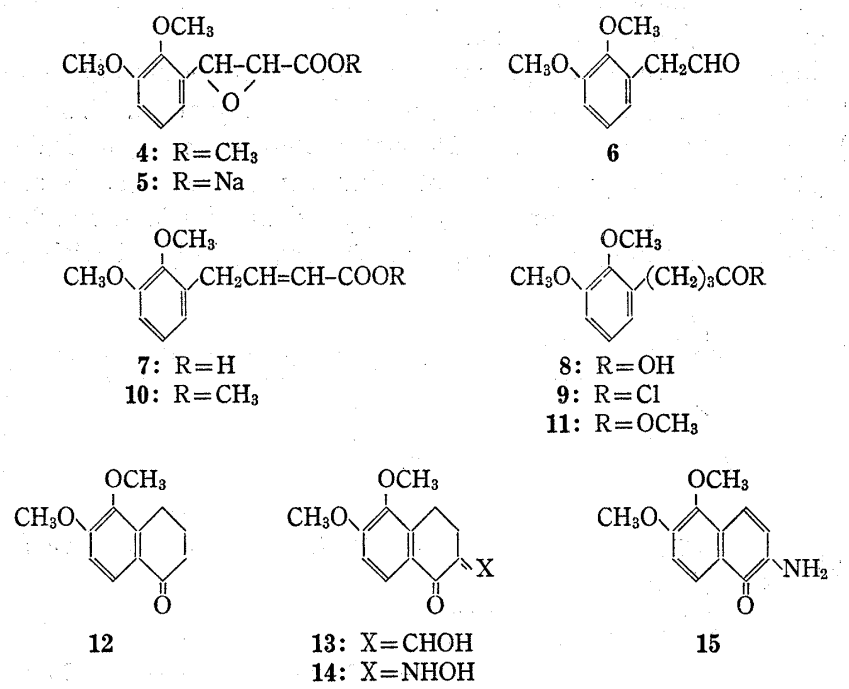

Chart 2

The rigid derivative of noradrenaline (**1**) was synthesized from **15** by demethylation with hydrobromic acid affording 2-amino-5,6-dihydroxy-3,4-dihydro-1(2H)-naphthalenone (**16**) followed by catalytic reduction over platinium dioxide. In the nuclear magnetic resonance (NMR) spectrum of **1**·hydrobromide, the proton signal at the 1-position appeared as two overlapped doublets at δ 4.57 (J=1 Hz) and δ 4.50 (J=9 Hz). From the coupling constants and intensities of each band **1** was assumed to be *ca.* 1 : 2 mixture of 1,2-*cis* and 1,2-*trans* derivatives.

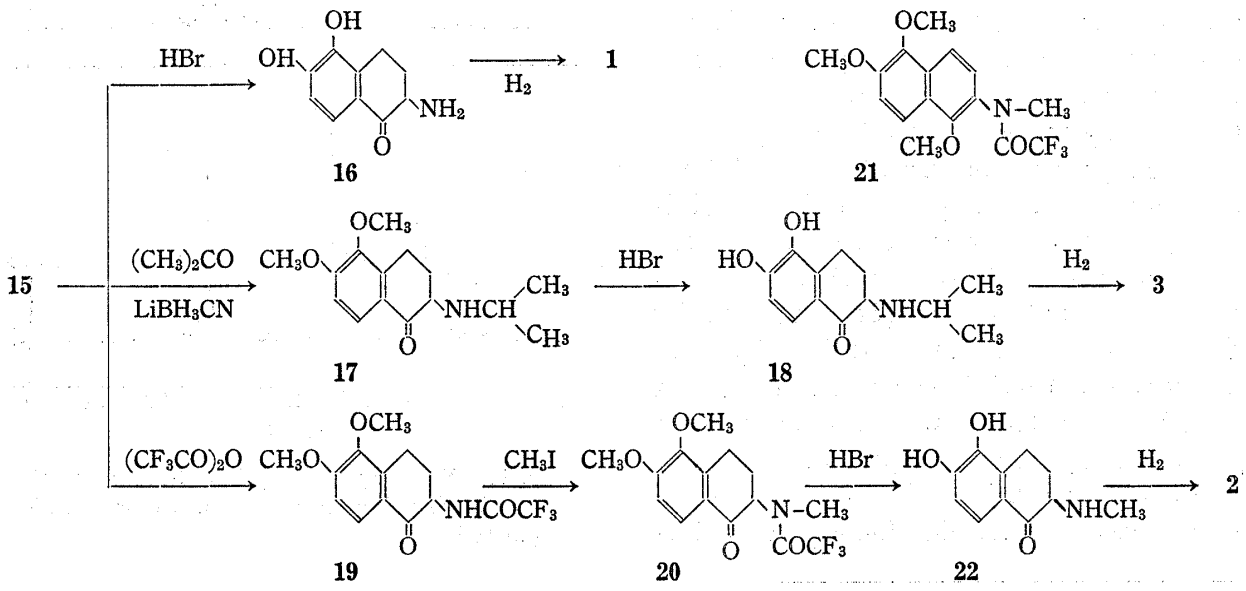

Chart 3

On the other hand, N-isopropylidene derivative of **15**, prepared *in situ* from **15** and acetone, was reduced with lithium cyanoborohydride[5] to give the corresponding N-isopropyl derivative (**17**) leaving the 1-carbonyl group unaffected. Demethylation of **17** affording 5,6-dihydroxy derivative (**18**) followed by catalytic reduction yielded **3**, the rigid derivative of isoproterenol. The NMR spectrum of **3** showed that the compound was also a mixture of 1,2-*cis* and *trans* isomers, the ratio of each being about 1:3.

The adrenaline derivative (**2**) was prepared *via* a detour of the similar route, since reductive methylation of **15** with formaldehyde resulted in N,N-dimethylation. Thus, N-trifluoroacetyl derivative (**19**), obtained by treatment of **15** with trifluoroacetic anhydride, was allowed to react with methyl iodide in the presence of potassium carbonate to give N-methyl-N-trifluoroacetate (**20**) in 70% yield, accompanied by a 22% yield of 1,5,6-trimethoxy-N-methyl-N-trifluoroacetyl-2-naphthylamine (**21**). Compound **20** was hydrolyzed with hydrobromic acid

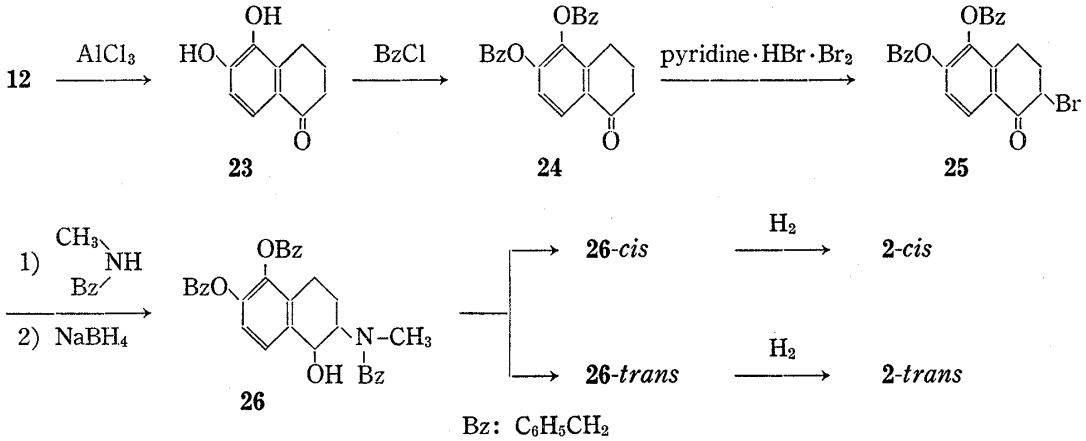

Chart 4

to give 5,6-dihydroxy-2-methylamino-3,4-dihydro-1(2H)-naphthalenone (**22**), which was led to **2** by catalytic reduction.

In the NMR spectrum of **2**, the proton at the 1-position appeared as a broad signal, indicating that **2** prepared by the above method was also a mixture of *cis* and *trans* isomers. In all cases of **1**, **2**, and **3**, the separation of each isomer from the mixture by such means as recrystallization or chromatography proved to be difficult.

The synthesis of pure *dl-cis* and *dl-trans* compounds of **2**, designated as **2**-*cis* and **2**-*trans* respectively, was carried out by the following route. 5,6-Dibenzyloxy-3,4-dihydro-1(2H)-naphthalenone (**24**), obtained by demethylation of **12** affording 5,6-dihydroxy derivative (**23**) and the subsequent treatment with benzyl chloride, was brominated with pyridinium hydrobromide perbromide to give α-bromoketone (**25**). The reaction of **25** with benzylmethylamine followed by reduc-

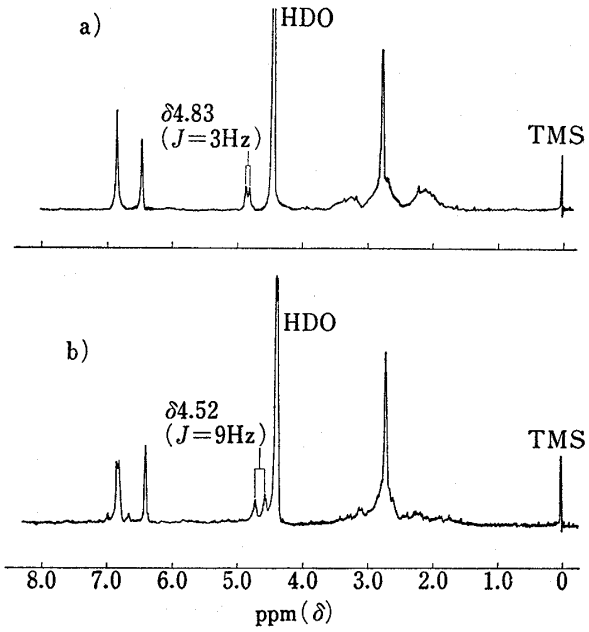

Fig. 1. NMR Spectra of **2**-*cis* Fumarate (a) and **2**-*trans* Fumarate (b) in DMSO-d_6+D_2O (60 MHz)

5) R.F. Borch, M.D. Bernstein, and H.D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

tion with sodium borohydride afforded a *cis* and *trans* mixture of 2-(N-benzyl-N-methylamino)-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (**26**). It was found that only **26**-*trans* was crystallized from a benzene solution of **26** upon addition of methanol. The NMR spectrum of **26**-*trans* showed a doublet at δ 4.67 (J=10 Hz). A column chromatography of the mother liquor on silica gel afforded **26**-*cis* whose NMR spectrum showed a doublet at δ 4.82 (J=3.0 Hz). After recrystallization, **26**-*trans* and **26**-*cis* were respectively led to **2**-*trans* and **2**-*cis* by catalytic hydrogenation over palladium-charcoal.

As has been reported previously,[2] compounds **1**, **2**, and **3** showed potent β-adrenoceptor activities with predominant β_2-directing property. The β_2-adrenoceptor activity of **3**, a racemic *trans* and *cis* mixture, was found to surpass that of *l*-isoproterenol. It should be noted that even the compound **1**, a cyclic derivative of noradrenaline, showed virtually no α-adrenergic activity. As for the β-activities of the two stereoisomers of **2**, **2**-*trans* was about ten times as potent as **2**-*cis*. These results, as well as the fact that the activities of 2-alkylamino-6,7-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols were very weak,[6,7] appear to suggest that the fixation of the side chain of catecholamine into 5,6-dihydroxytetrahydronaphthalene ring brings about a favorable arrangement of functional groups in the molecule for the selective interaction with the β-adrenergic receptor. Further studies in this field are in progress.

Experimental

All melting points were measured on a micro hot-stage apparatus and are uncorrected. Samples for microanalysis were dried over P_2O_5 *in vacuo* for 5 hr. Infrared (IR) spectra were taken with a Hitachi 215 spectrophotometer. NMR spectra were recorded with Varian T-60 or HA-100 using Me_4Si as external standard when the solvent was D_2O, or otherwise as internal standard.

Methyl 3-(2,3-Dimethoxyphenyl)glycidate (4)——To a solution of MeONa prepared *in situ* from Na (10.5 g) and abs. MeOH (150 ml) was added dropwise a mixture of 2,3-dimethoxybenzaldehyde (50 g) and methyl chloroacetate (50 g) with vigorous stirring at −10°. After the addition was completed, stirring was continued for 2 hr at −5° and further 3 hr at room temperature. The reaction mixture was poured into ice-water (700 ml) containing 4 ml of AcOH. Resulting oily substance was extracted with benzene and the extract, dried over anhydrous Na_2SO_4, was evaporated. Distillation of the residue under reduced pressure afforded 57.4 g (80%) of **4** as colorless oil, $bp_{0.5}$ 136—138°. *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.40; H, 6.14. NMR (in $CDCl_3$) δ: 3.48 (1H, d, J=2.5 Hz), 3.83 (3H, s), 3.86 (6H, s), 4.40 (1H, d, J=2.5 Hz).

Sodium 3-(2,3-Dimethoxyphenyl)glycidate (5)——To a solution of **4** (57.4 g) in abs. benzene (300 ml) was added at 5° a solution of MeONa prepared from Na (5.6 g) and abs. MeOH (78 ml). After standing the mixture at 10° for 10 min, to which was added H_2O (5 ml) and the resulting colorless precipitate was collected by filtration to give 45.5 g (76.5%) of **5**. A part of the sample recrystallized from H_2O–MeOH–EtOH (2: 9: 9) showed mp 261—267° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}O_5Na$: C, 53.66; H, 4.50; Na, 9.34. Found: C, 53.86; H, 4.58; Na, 9.39. NMR (in D_2O) δ: 3.42 (1H, d, J=2.4 Hz), 3.73 (3H, s), 3.77 (3H, s), 4.15 (1H, d, J=2.4 Hz), 6.50—7.10 (3H, m).

2,3-Dimethoxyphenylacetaldehyde (6)——To a solution of **5** (45.4 g) in H_2O (80 ml) was added AcOH (10.7 ml) and benzene (128 ml), and the mixture was warmed at 80° with stirring until the evolution of CO_2 ceased. After cooling, the benzene layer was separated and the aqueous phase was extracted four times with 200 ml portions of benzene. The combined benzene solution was dried over anhydrous Na_2SO_4 and evaporated. Distillation of the residue gave 25.5 g (77%) of **6** as colorless oil, $bp_{0.3}$ 88—90°. *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.15; H, 6.71. Found: C, 66.91; H, 6.68. NMR (in $CDCl_3$) δ: 3.65 (2H, d, J=2.4 Hz), 3.80 (3H, s), 3.84 (3H, s), 6.60—7.10 (3H, m), 9.68 (1H, t, J=2.4 Hz).

Methyl 4-(2,3-Dimethoxyphenyl)-2-butenoate (10)——A solution of **6** (130 g) and carbomethoxymethylenetriphenylphosphorane (259 g) in anhydrous benzene (1 liter) was refluxed for 2 hr. After benzene was evaporated *in vacuo*, the residue was shaken with petroleum ether (5 liters) and the resulting crystals were removed by filtration. The filtrate was evaporated and the residue was distilled under reduced pressure to give 158 g (93%) of **10** as colorless oil, $bp_{0.7}$ 146—148°. *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.86; H, 6.83. NMR (in $CDCl_3$) δ: 3.51 (2H, q), 3.66 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 5.75 (1H, q), 6.58—7.34 (4H, m).

Methyl 4-(2,3-Dimethoxyphenyl)butanoate (11)——A solution of **10** (156 g) in AcOH (500 ml) was subjected to catalytic reduction over 5% Pd–C (50 g) under ordinary temperature and pressure. After removal

6) R.I. Thrift, *J. Chem. Soc.* (*C*), **1967**, 288.
7) M. Kanno, private communication.

of the catalyst by filtration and evaporation of AcOH, the residue was taken up in AcOEt. The AcOEt solution was washed with 5% aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated. Distillation of the residue under reduced pressure afforded 150 g (95%) of **11** as colorless oil, bp_3 134° (lit.[4] bp_2 112°). NMR (in $CDCl_3$) δ: 1.76—2.88 (6H, m), 3.66 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 6.66—7.16 (3H, m). IR ν_{max}^{liquid} cm^{-1}: 2950, 2840, 1735, 1585, 1480, 1270, 1220, 1080, 1010, 745. The NMR and IR spectra showed complete identity with those of a sample prepared according to the literature.[4]

4-(2,3-Dimethoxyphenyl)-2-butenoic Acid (7)——To a solution of malonic acid (23 g) and piperidine (1 g) in pyridine (20 ml) was added dropwise a solution of **6** (19.5 g) in pyridine (30 ml) at room temperature. The mixture was warmed at 40° until evolution of CO_2 ceased. After the temperature was raised to 80° for a few minutes, the reaction mixture was poured into ice-water (200 ml) containing 65 ml of conc. HCl and the resulting oil was extracted five times with 200 ml portions of $CHCl_3$. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to give 25 g of **7** as pale yellow oil, which was used for the subsequent reaction without further purification. NMR (in $CDCl_3$) δ: 3.78 (3H, s), 3.82 (3H, s), 11.2 (1H, broad s). IR ν_{max}^{liquid} cm^{-1}: 1720 (COOH).

4-(2,3-Dimethoxyphenyl)butanoic Acid (8)——i) A suspension of **11** (308 mg) in 5% aq. KOH (4 ml) was heated under reflux for 70 min. After cooling, the mixture was extracted with $CHCl_3$. The aqueous phase was acidified with 3 N HCl, and resulting crystals were taken up in $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from benzene–petroleum ether (1: 3) to give 265 mg (92.5%) of **8** as colorless crystals, mp 60—62°, which showed no depression of mp on admixture with an authentic sample prepared according to the literature.[4] NMR (in $CDCl_3$) δ: 1.74—2.88 (6H, m), 3.82 (3H, s), 3.84 (3H, s), 6.64—7.23 (3H, m), 9.70—10.00 (1H, broad s). IR ν_{max}^{KBr} cm^{-1}: 2800—3000, 1720, 1610, 1595, 1490, 1355, 1285, 1230, 1220, 1085, 1020, 780.

ii) A solution of **7** (25 g) in AcOH (200 ml) was subjected to catalytic reduction over PtO_2 (3.5 g) at room temperature under ordinary pressure. After filtration of the catalyst and evaporation of the solvent, the residue was taken up in benzene (250 ml). The benzene solution was extracted with 10% aq. Na_2CO_3 (150 ml). The extract was acidified with 3 N HCl and extracted three times with 200 ml portions of $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to give 24.7 g of **8**, the NMR and IR spectra of which was identical with those of the sample prepared in i).

5,6-Dimethoxy-3,4-dihydro-1(2H)-naphthalenone (12)——i) To a solution of **8** (11.2 g) in abs. benzene (50 ml) was added by portions powdered PCl_5 (12.5 g) and the mixture was stirred for 1 hr at room temperature to afford a solution of 4-(2,3-dimethoxyphenyl)butyryl chloride (**9**). To this solution, cooled below 50°, was added a solution of $SnCl_4$ (20 g) in abs. benzene (25 ml). After stirred for 6 min, the mixture was poured into a mixture of conc. HCl (60 ml), ether (60 ml) and ice (100 g). The organic layer was separated, washed with 10% aq. NaOH and H_2O, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from cyclohexane afforded 9.5 g (92%) of **12** as colorless pillars, mp 104—105°, which showed complete identity with an authentic sample[4] in every respect.

ii) A mixture of **8** (21 g) and polyphosphoric acid (PPA) (105 g) was warmed at 50° with stirring. After 5 min, 40 g of PPA was added and the reaction was continued for another 5 min. The reaction mixture was poured into ice-water and extracted with $CHCl_3$ (200 ml × 3). The extract was washed with saturated aq. NaCl, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from cyclohexane furnished 11.4 g of **12**.

2-Hydroxymethylene-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (13)——To a mixture of abs. benzene (70 ml), ethyl formate (7.2 g) and powdered MeONa which was prepared from Na (2.26 g) and abs. MeOH (50 ml), was added dropwise a solution of **12** (10 g) in abs. benzene (55 ml) with stirring at 2—3° under a stream of nitrogen. After the mixture was stirred for 4 hr at 2—5° and further for 1 hr at room temperature, to the mixture was added ice-water (200 ml) and $CHCl_3$ (200 ml). The aqueous layer was separated, neutralized with 3 N HCl, and extracted four times with 200 ml portions of $CHCl_3$. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from cyclohexane gave 8.7 g (76.5%) of **13** as pale yellow needles, mp 83—83.5°. *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.73; H, 6.22.

2-Hydroxyimino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (14)——To a solution of **13** (2.34 g) in a mixture of CH_2Cl_2 (30 ml), AcOH (150 ml) and H_2O (7.5 ml) was added dropwise a solution of $NaNO_2$ (1.38 g) in H_2O (19 ml) with stirring at 0—1°. After the addition was completed, the mixture was stirred at 0—1° for 30 min and diluted with CH_2Cl_2 (200 ml). The CH_2Cl_2 layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from AcOEt to give 1.96 g (83.5%) of **14** as pale yellow needles, mp 170—182° (gradually decomposed). *Anal.* Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.21; H, 5.64; N, 5.83.

2-Amino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (15)——A solution of **14** (6 g) in a mixture of EtOH (300 ml) and conc. HCl (4 ml) was subjected to catalytic reduction over 5% Pd–C (3 g) under ordinary temperature and pressure until the absorption of hydrogen stopped. After the crystals deposited in the mixture were dissolved by adding EtOH (200 ml) and warming, the mixture was decolorlized by treatment with activated charcoal (*ca.* 10 g) and filtered while hot. The filtrate was concentrated to about

50 ml and cooled. Resulting crystals were filtered and recrystallized from EtOH to give 4.1 g (62%) of **15**, which was identical in every respect with an authentic sample prepared according to the literature.[3]

2-Amino-5,6-dihydroxy-3,4-dihydro-1(2H)-naphthalenone Hydrobromide (16)——A mixture of **15** (3.1 g) and 47% HBr (50 ml) was refluxed for 3 hr with stirring. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in hot MeOH (150 ml). To this solution was added AcOEt until a turbidity appeared. On standing the mixture in a refrigerator, 3.1 g (97%) of **16** was deposited as colorless granules, mp>300° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_3N \cdot HBr$: C, 43.82; H, 4.41; N, 5.11. Found: C, 43.65; H, 4.64; N, 5.01. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O).

2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol Hydrobromide (1)——A solution of **16** (200 mg) in H_2O (5 ml) was catalytically reduced over PtO_2 (50 mg) under ordinary temperature and pressure until 1 eq. hydrogen was absorbed. The catalyst was removed by filtration, while the filtrate was dropped into 100 ml of ether. To the ethereal mixture was added MeOH until a homogeneous solution was obtained. On cooling the solution, 100 mg (50%) of **1** was crystallized as colorless prisms, mp 190—200°(decomp.). *Anal.* Calcd. for $C_{10}H_{13}O_3N \cdot HBr \cdot H_2O$: C, 40.84; H, 5.48; N, 4.76. Found: C, 40.49; H, 5.37; N, 4.61. NMR (in DMSO-d_6+D_2O) δ: 1.6—3.4 (5H, m), 4.5 (0.7H, d, J=9 Hz), 4.57 (0.3H, d, J=1 Hz), 6.6—6.9 (2H, m).

2-Isopropylamino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (17)——To a solution of **15** (75 mg) in anhydrous acetone (3 ml) and abs. EtOH (5 ml) was added by portions $LiBH_3CN \cdot 2$ dioxane[8] (80 mg) at 0°. After stirred at 0° for 3 hr, the mixture was acidified with dil. HCl and evaporated *in vacuo*. The residue was neutralized with 5% aq. $NaHCO_3$, and extracted three times with 10 ml portions of ether. After the extract was washed with H_2O and dried over Na_2SO_4, through which was passed dry HCl. Ether was evaporated and the residue was recrystallized from EtOH–ether to give 70 mg (81%) of **17** as colorless granules, mp 170—172° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}O_3N \cdot HCl$: C, 60.09; H, 7.40; N, 4.07. Found: C, 59.70; H, 7.48; N, 4.62. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O). NMR (in D_2O) δ: 1.47 (6H, d, J=7 Hz), 3.85 (3H, s), 4.00 (3H, s), 7.13 (1H, m), 7.85 (1H, m).

5,6-Dihydroxy-2-isopropylamino-3,4-dihydro-1(2H)-naphthalenone Hydrobromide (18)——A mixture of **17** (200 mg), 48% HBr (2 ml) and AcOH (0.75 ml) was heated in a sealed tube for 2 hr at 140—150°. The resulting mixture was diluted with 2 ml of H_2O, decolorized with activated charcoal, and filtered. The filtrate was concentrated *in vacuo* to afford 153 mg (72%) of **18** as colorless crystals, mp 220—224° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_3N \cdot HBr$: C, 49.38; H, 5.74; N, 4.43. Found: C, 49.24; H, 5.67; N, 4.19. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR (in D_2O) δ: 1.64—1.58 (6H, m), 2.00—4.60 (6H, m), 6.92 (1H, d, J=8 Hz), 7.54 (1H, d, J=8 Hz).

5,6-Dihydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (3)——A solution of **18** (180 mg) in 10 ml of H_2O was subjected to catalytic reduction over 5% Pd–C (200 mg) at room temperature under ordinary pressure. After 1 eq. hydrogen was absorbed, the catalyst was removed by filtration and the filtrate was lyophilized. Recrystallization of the residue from EtOH–ether (1: 2) gave 160 mg (88%) of **3** as colorless prisms, mp 167—169° (decomp.). *Anal.* Calcd. for $C_{13}H_{19}O_3N \cdot HBr \cdot H_2O$: C, 46.44; H, 6.59; N, 4.16. Found: C, 46.50; H, 6.02; N, 3.97. NMR (in DMSO-d_6+D_2O) δ: 1.35 (6H, m), 1.5—3.5 (6H, m), 4.63 (1H, m), 6.7—6.9 (2H, m).

5,6-Dimethoxy-2-trifluoroacetamido-3,4-dihydro-1(2H)-naphthalenone (19)——A mixture of **15** (2 g) and trifluoroacetic anhydride (50 g) was allowed to stand at room temperature for 30 min. To the resulting solution was added ether (50 ml) to precipitate colorless leaflets. After 100 ml of *n*-hexane was added to the mixture and cooled in order to complete the crystallization, the crystals were filtered to afford 2.4 g (97.5%) of **19**, mp 166—167°. *Anal.* Calcd. for $C_{14}H_{14}O_4NF_3$: C, 52.98; H, 4.45; N, 4.42. Found: C, 52.54; H, 4.38; N, 4.14. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1700 (C=O), 1670 (C=O).

2-(N-Methyltrifluoroacetamido)-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (20) and N-Trifluoroacetyl-N-methyl-1,5,6-trimethoxy-2-naphthylamine (21)——A mixture of **19** (1.5 g), K_2CO_3 (5 g), methyl iodide (3 g), and oxygen-free acetone (150 ml) prepared by bubbling nitrogen gas, was vigorously stirred at room temperature for 2 days under a stream of nitrogen. After insoluble substance was removed by filtration, the filtrate was dissolved in $CHCl_3$ (10 ml) and submitted to a column chromatography on silica gel eluting with $CHCl_3$–ether (20: 1). Each fraction was traced by thin-layer chromatography. Evaporation of the first eluate and recrystallization of the residue from *n*-hexane gave 0.4 g (22%) of **21** as colorless prisms, mp 108—109°. *Anal.* Calcd. for $C_{16}H_{16}O_4NF_3$: C, 55.97; H, 4.70; N, 4.08. Found: C, 56.04; H, 4.73; N, 4.24. The treatment of the second eluate and recrystallization from *n*-hexane–EtOH (1: 1) afforded **20** as colorless granules, mp 149—151°. *Anal.* Calcd. for $C_{15}H_{16}O_4NF_3$: C, 54.38; H, 4.87; N, 4.23. Found: C, 54.23; H, 4.74; N, 4.14. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1670 (C=O).

5,6-Dihydroxy-2-methylamino-3,4-dihydro-1(2H)-naphthalenone Hydrobromide (22)——A mixture of **20** (500 mg) and 47% HBr (20 ml) was refluxed for 3 hr. To the cooled mixture was added activated charcoal and oxygen-free MeOH (50 ml), and the whole mixture was refluxed for 10 min. After filtration, the filtrate was evaporated *in vacuo* and the residue was dissolved in MeOH (20 ml). To the solution was added dropwise ether (100 ml) and cooled with ice-water to precipitate **22** as colorless granules, mp 225—228° (decomp.).

8) W. Wittig and P. Raff, *Ann.*, **573**, 195 (1951).

Yield: 430 mg (98%). *Anal.* Calcd. for $C_{11}H_{13}O_3N \cdot HBr$: C, 45.85; H, 4.55; N, 4.86. Found: C, 45.87; H, 5.05; N, 4.68. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O).

5,6-Dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol Hydrobromide (2)——A solution of **22** (200 mg) in H_2O (3 ml) was subjected to catalytic reduction over PtO_2 (50 mg) under ordinary temperature and pressure. After 1 eq. hydrogen was absorbed, the mixture was filtered into oxygen-free ether (100 ml). To the filtrate was added MeOH until a clear homogeneous solution was obtained. And then, to the solution was added ether until it began to become a little turbid. On standing the solution in a refrigerator, **2** was crystallized as colorless granules, mp 165—169° (decomp.). Yield: 130 mg (63%). *Anal.* Calcd. for $C_{11}H_{15}O_3N \cdot HBr \cdot 1/2H_2O$: C, 44.16; H, 5.40; N, 4.68. Found: C, 44.11; H, 5.40; N, 4.45. NMR (in DMSO-d_6+D_2O) δ: 2.7 (3H, s), 1.6—3.3 (5H, m). 4.4—4.8 (1H, broad m), 6.6—6.9 (2H, m).

5,6-Dihydroxy-3,4-dihydro-1(2H)-naphthalenone (23)——A mixture of **12** (3.1 g), anhydrous $AlCl_3$ (9.0 g) and abs. benzene (60 ml) was refluxed for 2 hr. To the cooled mixture was added small amount of ice and 18 ml of 3 N HCl (18 ml). The resulting crystals were collected by filtration, washed with H_2O, and recrystallized from hot H_2O (1 liter) to give 2.3 g (85%) of colorless needles, mp 198—199°. *Anal.* Calcd. for $C_{10}H_{10}O_3 \cdot 1/4H_2O$: C, 65.75; H, 5.79. Found: C, 65.78; H, 5.79. IR ν_{max}^{KBr} cm^{-1}: 3600—3400, 3200—2300 (OH), 1640 (C=O).

5,6-Dibenzyloxy-3,4-dihydro-1(2H)-naphthalenone (24)——To a solution of **23** (10.0 g) in EtOH (300 ml) was added powdered K_2CO_3 (8.6 g), KI (10.4 g), $Na_2S_2O_3 \cdot 5H_2O$ (0.5 g), and benzyl chloride (15 g) with stirring under a stream of nitrogen, and the mixture was heated on an oil bath under reflux for 1.5 hr. After a solution of KOH (3.5 g) in EtOH (50 ml) was added, the mixture was refluxed for further 2.5 hr and then the solvent was removed *in vacuo*. To the residue was added 300 ml of H_2O and extracted three times with 300 ml portions of $CHCl_3$. The extract was washed with H_2O, dried over anhydrous $MgSO_4$, decolorized with activated charcoal, and evaporated *in vacuo*. Recrystallization of the residue from MeOH (250 ml) gave 17.3 g (86%) of **24** as colorless leaflets, mp 104—106°. *Anal.* Calcd. for $C_{24}H_{22}O_3$: C. 80.42; H, 6.19. Found: C, 79.81; H, 6.16. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O).

5,6-Dibenzyloxy-2-bromo-3,4-dihydro-1(2H)-naphthalenone (25)——To a solution of **24** (716 mg) in $CHCl_3$ (20 ml) was added pyridinium hydrobromide perbromide (703 mg) and the mixture was heated at 60—65° for 5 min with vigorous stirring. After cooling, benzene (100 ml) was added to the reaction mixture and the mixture was poured into ice-water (100 ml). The benzene layer was separated, washed four times with 100 ml portions of ice-water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The resulting pale brown oil was purified by a column chromatography over silica gel (80 g) using benzene as eluent to give 440 mg (50%) of **25** as colorless needles, mp 106—108°. *Anal.* Calcd. for $C_{24}H_{21}O_3Br$: C, 65.91; H, 4.84. Found: C, 65.78; H, 4.75. IR ν_{max}^{KBr} cm^{-1}: 1680, 1590.

cis*- and *trans*-2-(N-Benzyl-N-methylamino)-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (26-*cis* and *trans*)**——To a solution of **25** (13.4 g) in tetrahydrofuran (THF) (200 ml) was added benzylmethylamine (13.4 g) and the mixture was refluxed for 18 hr under nitrogen. After evaporating the solvent *in vacuo*, the residue was taken up in benzene (50 ml). The benzene solution was washed with cooled 2% HCl (200 ml) and subsequently three times with 200 ml portions of cold water, dried over anhydrous $MgSO_4$, and evaporated. The resulting dark brown oil was dissolved in a mixture of THF (50 ml) and EtOH (150 ml). To the solution, ice-cooled and stirred, was added $NaBH_4$ (2.6 g) under nitrogen. After 25 min, ice bath was removed and the temperature was raised up to room temperature. After 3 hr, excess $NaBH_4$ was decomposed by dropwise addition of AcOH. The mixture was diluted with EtOH (100 ml) and allowed to stand overnight at −20° to deposit a *cis* and *trans* mixture of **26**, which was dissolved in benzene (100 ml). After the benzene solution was concentrated to about 15 ml, to the solution was added MeOH (150 ml). The resulting crystals were filtered and recrystallized from $CHCl_3$–MeOH to give 4.3 g (30%) of **26-*trans as leaflets, mp 116—117°. *Anal.* Calcd. for $C_{32}H_{33}O_3N$: C, 80.13; H, 6.94; N, 2.92. Found: C. 79.75; H, 6.81; N, 2.81. NMR (in $CDCl_3$) δ: 2.27 (3H), 3.48 (1H, s, J=10 Hz), 3.78 (1H, d, J=13 Hz), 4.67 (1H, d, J=10 Hz), 4.8 (1H, broad), 5.03 (2H, s), 5.13 (2H, s).

The mother liquor of the crude **26-*trans*** was evaporated and the residue was chromatographed over silica gel (70 g). After successive elution with benzene (200 ml), benzene–$CHCl_3$ (1: 1, 200 ml), and $CHCl_3$, the main fraction was evaporated. Recrystallization of the residue from $CHCl_3$–*n*-hexane (1: 10) afforded 2.2 g (15%) of **26-*cis*** as pale yellow leaflets, mp 118—120°. NMR (in $CDCl_3$) δ: 2.28 (3H, s), 3.60 (1H, d, J=14 Hz), 3.83 (1H, d, J=14 Hz), 4.80 (1H, broad), 4.82 (1H, d, J=3 Hz), 5.00 (2H, s), 5.10 (2H, s). Mass Spectrum: 479 (M^+), 388 ($M-C_6H_5CH_2^+$).

trans*-5,6-Dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol (2-*trans*)**——i) A solution of **26-*trans (1.1 g) in a mixture of THF (10 ml) and EtOH (20 ml) was catalytically reduced over 10% Pd-C (200 mg) under ordinary temperature and pressure. When about 3 eq. hydrogen was absorbed (after *ca.* 4 hr), the catalyst was filtered off, while the filtrate was dropped into a solution of fumaric acid (190 mg) in ether (450 ml). The mixture was evaporated *in vacuo*. The oily residue was taken up in 80% EtOH (25 ml), decolorized with activated charcoal, diluted with ether (200 ml), and allowed to stand overnight at 5°. The resulting colorless crystals were collected by filtration to give 171 mg (28%) of **2-*trans*** fumarate, mp 199° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}O_3N \cdot 1/2C_4H_4O_4 \cdot H_2O$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.51; H, 6.72; N, 4.73. NMR (in DMSO-d_6) δ: 2.55 (3H, s), 1.4—3.1 (6H, m), 4.52 (1H, d, J=9 Hz), 6.38 (2H×1/2, s, olefin protons of fumaric acid), 6.78 (1H, d, J=9 Hz), 6.85 (1H, d, J=9 Hz), 6.4—6.9 (4H, m).

ii) The catalytic reduction was conducted using **26**-*trans* (682 mg), THF (20 ml), EtOH (15 ml) and 10% Pd–C (100 mg) under the same condition as in i). After filtration of the catalyst, a mixture of 47% HBr (0.17 ml) and EtOH (2 ml) was added to the filtrate and concentrated to 5 ml. To the solution was added ether (500 ml) and the mixture was allowed to stand in a refrigerator. The resulting precipitate was filtered to give 265 mg (64%) of **2**-*trans* hydrogen bromide as pale blue powder, mp 188—192° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}O_3N \cdot HBr$: C, 45.53; H, 5.56; N, 4.83. Found: C, 45.83; H, 5.70; N, 4.73.

***cis*-5,6-Dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol (2-*cis*)**——**26**-*cis* (1.1 g) was subjected to catalytic reduction under the same condition as above. After filtration of the catalyst, the filtrate was added dropwise to a solution of fumaric acid in 15 ml of EtOH. To the mixture was added in turn ether (30 ml), EtOH (10 ml) and H_2O (6 ml), and the solution was allowed to stand overnight at 5°. Recrystallization of the resulting crystals from a mixture of H_2O (10 ml) and acetone (100 ml) afforded 315 mg (51%) of **2**-*cis* fumarate, mp 195° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}O_3N \cdot 1/2C_4H_4O_4$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.20; H, 6.26; N, 5.47. NMR (in DMSO-d_6) δ: 2.53 (3H, s), 1.7—3.2 (6H, m), 4.83 (1H, d, $J=3$ Hz), 6.33 (1H, s), 6.60 (2H, s), 6.9 (4H, broad).

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