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-dibenzoxylhydrazine materials via cis- and trans-2-(N-benzyl-N-methylamino)-5,6-dibenzoxylhydrazine-1,2,3,4-tetrahydro-1-naphthalenol (26-cis and 26-trans).

Keywords—catecholamine; tetrahydrornaphthalene; tetrahydronaphthylamine; \( \beta \)-adrenoceptor; \( \beta _{2} \)-adrenergic activity; rigid catecholamine derivative

In the preceding report, 2) we described the potent \( \beta \)-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.

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-butenolic 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 boromethoxymethylenetriphenylphosphorane affording methyl 4-(2,3-dimethoxyphenyl)-2-butenolate (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 \( \alpha \)-oximino ketone (14) have been reported to result in unsatisfactory yields, 5) it was found that the process was markedly improved by conducting the conversion in two stages by way of \( \alpha \)-hydroxymethylene ketone (13).

1) Location: Juso, Yodogawa-ku, Osaka, 532, Japan.
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.

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CH₂OH
4: R=CH₃
5: R=Na

CH₂OH
7: R=H
10: R=CH₃

CH₂O
12

CH₂O
13: X=CHOH
14: X=NHOOH

CH₂O
15: NH₂
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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 platinum 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.

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15

16

17

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22
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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 \(N_2N\)-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 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-Dibenzzyloxy-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 \(\alpha\)-bromoketone (25). The reaction of 25 with benzylmethylamine followed by reduc-

\[ \text{Fig. 1. NMR Spectra of 2-cis Fumarate (a) and 2-trans Fumarate (b) in DMSO-\(d_6+D_2O \) (60 MHz)} \]

\[ \delta 4.52 \quad (J=9Hz) \]

\[ \delta 4.83 \quad (J=3Hz) \]

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tion with sodium borohydride afforded a cis and trans mixture of 2-(N-benzyl-N-methylamino)-5,6-dibenzoyloxy-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 \( \delta 4.67 \) (J = 10 Hz). A column chromatography of the mother liquor on silica gel afforded 26-cis whose NMR spectrum showed a doublet at \( \delta 4.82 \) (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, \(^6\) compounds 1, 2, and 3 showed potent \( \beta \)-adrenoceptor activities with predominant \( \beta_2 \)-directing property. The \( \beta_2 \)-adrenoceptor activity of 3, a racemic trans and cis mixture, was found to surpass that of \( \alpha \)-isoproterenol. It should be noted that even the compound 1, a cyclic derivative of noradrenaline, showed virtually no \( \alpha \)-adrenergic activity. As for the \( \beta \)-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, \(^7\) appear to suggest that the fixation of the side chain of catecholamine into 5,6-dihydroxytetrahydroanaphthalene ring brings about a favorable arrangement of functional groups in the molecule for the selective interaction with the \( \beta \)-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 \( \text{P}_2\text{O}_5 \) 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, Si as external standard when the solvent was D,O, 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 \(-10^\circ\). After the addition was completed, stirring was continued for 2 hr at \(-5^\circ\) 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 \( \text{Na}_2\text{SO}_4 \), was evaporated. Distillation of the residue under reduced pressure afforded 57.4 g (80%) of 4 as colorless oil, \( \text{bp}_{3,5} 136-138^\circ \). *Anal. Calcd. for C\(_{12}\)H\(_{14}\)O\(_2\): C, 60.50; H, 5.92. Found: C, 60.40; H, 6.14.*

**Sodium 3-(2,3-Dimethoxyphenyl)glycidate (5)**—To a solution of 4 (57.4 g) in abs. benzene (300 ml) was added at \( 5^\circ \) a solution of MeONa prepared from Na (5.6 g) and abs. MeOH (78 ml). After standing the mixture at \( 0^\circ \) for 10 min, to which was added H\(_2\)O (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\(_2\)O-MeOH-EtOH (2: 2: 9) showed mp 261-267\(^\circ\) (decomp.). *Anal. Calcd. for C\(_{13}\)H\(_{15}\)O\(_2\)Na: C, 53.66; H, 4.50; Na, 9.34. Found: C, 53.86; H, 4.58; Na, 9.39.*

**2,3-Dimethoxyphenylacetalddehyde (6)**—To a solution of 5 (45.4 g) in H\(_2\)O (80 ml) was added AcOH (10.7 ml) and benzene (128 ml), and the mixture was warmed at 80\(^\circ\) 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 \( \text{Na}_2\text{SO}_4 \) and evaporated. Distillation of the residue gave 25.5 g (77%) of 6 as colorless oil, \( \text{bp}_{3,5} 88-90^\circ \). *Anal. Calcd. for C\(_{14}\)H\(_{14}\)O\(_2\): C, 66.15; H, 6.71. Found: C, 66.91; H, 6.68.*

**Methyl 4-(2,3-Dimethoxyphenyl)-2-butoxyle (10)**—A solution of 6 (130 g) and carboxymethyl-enetriphenylphosphorane (250 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, \( \text{bp}_{3,5} 146-148^\circ \). *Anal. Calcd. for C\(_{27}\)H\(_{30}\)O\(_2\): C, 66.09; H, 6.83. Found: C, 65.86; H, 6.83.*

**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

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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. NaHCO₃ and H₂O, dried over Na₂SO₄, and evaporated. Distillation of the residue under reduced pressure afforded 150 g (95%) of 11 as colorless oil, bp₄ 134° (lit., bp₄ 112°). NMR (in CDCl₃) 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 νₓ max 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.¹

4-(2,3-Dimethoxyphenyl)-2-butenolic 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°C until evolution of CO₂ ceased. After the temperature was raised to 80°C 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 CHCl₃. The extract was washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated to give 25 g of 7 as pale yellow oil, which was used for the subsequent reaction without further purification. NMR (in CDCl₃) δ: 3.78 (3H, s), 3.82 (3H, s), 11.2 (1H, broad s). IR νₓ max 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 CHCl₃. The aqueous phase was acidified with 3N HCl, and the resulting crystals were taken up in CHCl₃. The CHCl₃ solution was dried over anhydrous Na₂SO₄ 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 according to the literature.² NMR (in CDCl₃) δ: 1.74—2.82 (6H, m), 3.82 (3H, s), 3.84 (3H, s), 6.64—7.23 (3H, m), 9.70—10.00 (1H, broad s). IR νₓ max 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 PtO₂ (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 dried with 10% aq. Na₂CO₃ (150 ml). The extract was acidified with 3N HCl and extracted three times with 200 ml portions of CHCl₃. The CHCl₃ solution was dried and evaporated to give 24.7 g of 8, the NMR and IR spectra of which were identical with those of the sample prepared in i).

5,6-Dimethoxy-3,4-dihydro-1(2H)-napthalenaldehyde (12)—i) To a solution of 8 (11.2 g) in abs. benzene (50 ml) was added by portions powdered PCl₅ (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°C, was added a solution of SnCl₂ (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 H₂O, dried over Na₂SO₄, and evaporated. Recrystallization of the residue from cyclohexane afforded 9.5 g (92%) of 12 as colorless pillars, mp 104—105°C, which showed complete identity with an authentic sample in every respect.

ii) A mixture of 8 (21 g) and polyphosphoric acid (PPA) (105 g) was warmed at 50°C 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 CHCl₃ (200 ml x 3). The extract was washed with saturated aq. NaCl, dried over Na₂SO₄, and evaporated. Recrystallization of the residue from cyclohexane furnished 11.4 g of 12.

2-Hydroxymethylene-5,6-dimethoxy-3,4-dihydro-1(2H)-napthalenaldehyde (13)—To a solution 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°C under a stream of nitrogen. After the mixture was stirred for 4 hr at 2—3°C and further for 1 hr at room temperature, the mixture was added ice-water (200 ml) and CHCl₃ (200 ml). The aqueous layer was separated, neutralized with 3N HCl, and extracted four times with 200 ml portions of CHCl₃. The extract was washed with H₂O, dried over anhydrous Na₂SO₄, and evaporated. Recrystallization of the residue from cyclohexane gave 8.7 g (76.5%) of 13 as pale yellow needles, mp 83—83.5°C. Anal. Calcd. for C₂₂H₂₆O₄: C, 66.65; H, 6.02. Found: C, 66.73; H, 6.22.

2-Hydroxymethylene-5,6-dimethoxy-3,4-dihydro-1(2H)-napthalenaldehyde 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 decolorized by treatment with activated charcoal (ca. 10 g) and filtered while hot. The filtrate was concentrated to about

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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.8

2-Amino-5,6-dihydroxy-3,4-dihydro-1(2H)-naphthalene-1-carboxylic acid (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 290-300° (decomp.). Anal. Calcd. for C15H14O2N⋅HBr⋅H2O: C, 43.82; H, 4.41; N, 5.11. Found: C, 43.65; H, 4.46; N, 5.01. IR νmax cm⁻¹: 1660 (C=O).

2-Amino-5,6-dihydroxy-1,3,4-tetrahydro-1-naphthalenol Hydrobromide (1) — A solution of 16 (200 mg) in H2O (5 ml) was rendered slightly alkaline over PtO2 (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 C15H14O2N⋅HBr⋅H2O: C, 40.84; H, 5.48; N, 4.78. Found: C, 40.49; H, 5.37; N, 4.41. NMR (in DMSO-d6 + D2O) δ: 1.6-3.4 (5H, m), 4.5 (0.7H, d, J = 9 Hz), 4.57 (0.3H, d, J = 1 Hz), 6.0-6.9 (2H, m).

2-Isopropylamino-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (17) — A solution of 25 (75 mg) in anhydrous acetone (3 ml) and abs. EtOH (5 ml) was added by portions to LiBH4CN:2 dioxane (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% eq. NaHCO3 and extracted three times with 10 ml portions of ether. After the extract was washed with H2O and dried over Na2SO4, the residue was recrystallized from EtOH-ether to give 70 mg (81%) of 17 as colorless granules, mp 170-172° (decomp.). Anal. Calcd. for C15H14O2N⋅HCl: C, 60.09; H, 7.40; N, 4.07. Found: C, 59.70; H, 7.48; N, 4.02. IR νmax cm⁻¹: 1695 (C=O). NMR (in D2O) 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-tetrahydro-1(2H)-naphthalenone Hydrobromide (18) — A mixture of 17 (200 mg), 43% 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 H2O, decolorized with activated charcoal, and filtered. The filtrate was concentrated in vacuo to afford 153 mg (79%) of 18 as colorless crystals, mp 220-224° (decomp.). Anal. Calcd. for C15H14O2N⋅HBr⋅H2O: C, 49.38; H, 5.74; N, 4.43. Found: C, 49.24; H, 5.67; N, 4.49. IR νmax cm⁻¹: 1680 (C=O). NMR (in D2O) 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-naphthalenone (3) — A solution of 18 (180 mg) in 10 ml of H2O 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 C15H14O2N⋅HBr⋅H2O: C, 46.44; H, 6.59; N, 4.16. Found: C, 46.50; H, 6.02; N, 3.97. NMR (in DMSO-d6 + D2O) δ: 1.35 (6H, m), 1.5-3.6 (5H, m), 4.63 (1H, m), 6.7-6.9 (2H, m).

5,6-Dimethoxy-2-trifluoracetamido-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 C15H14O2NF2: C, 52.08; H, 4.45; N, 4.42. Found: C, 52.54; H, 4.38; N, 4.14. IR νmax cm⁻¹: 3250 (NH), 1700 (C=O), 1670 (C=O).

2-(N-Methyltrifluoracetamido)-5,6-dimethoxy-3,4-dihydro-1(2H)-naphthalenone (20) and N-Trifluoroacetetyl-N-methyl-1,5,6-trimethoxy-2-naphthylamine (21) — A mixture of 19 (1.5 g), K2CO3 (5 g), methyl iodide (3 g), and oxygen-free acetone (150 ml) was prepared in a beaker by bubbling nitrogen gas, was vigorously stirred at room temperature for 2 days using a stream of nitrogen after insoluble substance was removed by filtration, the filtrate was distilled in CHCl3 (10 ml) and submitted to a column chromatography on silica gel eluting with CHCl3-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 105-110°. Anal. Calcd. for C15H14O2NF2: 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 C15H14O2NF2: C, 54.38; H, 4.87; N, 4.23. Found: C, 54.23; H, 4.74; N, 4.14. IR νmax 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 (2 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.).

Yield: 430 mg (98%). Anal. Calcd. for C₁₅H₂₀O₃N·HBr: C, 45.85; H, 4.55; N, 4.86. Found: C, 45.87; H, 5.05; N, 4.68. IR νmax cm⁻¹: 1660 (C=O).

5,6-Dihydr oxy-2-methylamino-1,2,3,4-tetra hydro-1-napthal enol Hydro bromide (2)—A solution of 22 (200 mg) in H₂O (3 ml) was added to a solution of the compound (100 mg) under nitrogen. The residue was filtered, washed with ether (3 ml), and dried. The residue was then recrystallized from hot H₂O (1 liter) to give 3.2 g (85%) of colorless needles, mp 165°-166° (decomp.). Yield: 130 mg (63%). Anal. Calcd. for C₁₅H₂₀O₃N·H₂O: C, 44.16; H, 5.40; N, 4.68. Found: C, 44.11; H, 5.40; N, 4.45. NMR (in DMSO-d₆ + D₂O) δ: 2.7 (3H, s), 1.6-3.3 (3H, m). 4.4-4.8 (1H, broad m), 6.6-6.9 (2H, m).

5,6-Dihy droxy-3,4-dihy dro-1(2H)-napthalen e nlone (23)—A mixture of 12 (3.1 g), anhydrous AlCl₃ (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 3N HCl (18 ml). The resulting crystals were collected by filtration, washed with H₂O, and recrystallized from hot H₂O (1 liter) to give 2.3 g (85%) of colorless crystals, mp 183°-184° (decomp.). Yield: 130 mg (63%). Anal. Calcd. for C₁₅H₂₀O₃N·H₂O: C, 65.75; H, 5.79. Found: C, 65.78; H, 5.79. IR νmax cm⁻¹: 3600-3400, 3200-2300 (OH), 1640 (C=O).

5,6-Di benzyloxy-3,4-dihy dro-1(2H)-napthal enolone (24)—A to a solution of 23 (100 g) in EtOH (300 ml) and 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 H₂O and extracted with ether. The residue 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. The benzene layer was separated, washed four times with 100 ml portions of ice-water, and evaporated in vacuo. The resulting residue was recrystallized from MeOH (250 ml) gave 17.3 g (86%) of 24 as colorless leaflets, mp 104°-108°. Anal. Calcd. for C₂₇H₂₂O₂: C, 80.42; H, 6.19. Found: C, 79.81; H, 6.16. IR νmax cm⁻¹: 1680 (C=O).

5,6-Di benzyloxy-2-bromo-3,4-dihy dro-1(2H)-napthal enolone (25)—To a solution of 24 (716 mg) in CHCl₃ (20 ml) and 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 water. The benzene layer was separated, washed four times with 100 ml portions of ice-water, and evaporated in vacuo in vacuo. The resulting pale brown oil was purified by a column chromatography over silica gel 80/120 using benzene as eluent to give 440 mg (50%) of 25 as colorless needles, mp 106°-108°. Anal. Calcd. for C₂₂H₂₀O₂Br: C, 65.91; H, 4.84. Found: C, 65.78; H, 4.75. IR νmax cm⁻¹: 1680, 1590.

cis- and trans-2-(N-Benzy l-N-methylamino)-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-napthal enol (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 MgSO₄, and evaporated in vacuo. The resulting brown oil was dissolved in a mixture of THF (50 ml) and EtOH (150 ml). To the solution, ice-cooled and stirred, was added NaBH₄ (2.6 g) under nitrogen. After 25 min, ice bath was removed and the temperature was raised to room temperature. After 3 hr, excess NaBH₄ was decomposed by dropwise addition of ACOH. The mixture was diluted with EtOH (100 ml) and allowed to stand overnight at -20°C 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 CHCl₃-MeOH to give 4.3 g (30%) of 26-trans as leaflets, mp 116°-117°. Anal. Calcd. for C₂₃H₂₁O₃N: C, 80.13; H, 6.94; N, 2.92. Found: C, 79.75; H, 6.81; N, 2.81. NMR (in CDCl₃) δ: 2.27 (3H, s), 3.48 (1H, s), J = 10 Hz, 3.75 (2H, d, J = 10 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-CHCl₃ (1:1, 200 ml), and CHCl₃, the major fraction was evaporated. Recrystallization of the residue from CHCl₃-n-hexane (1:10) afforded 2.2 g (15%) of 26-cis as pale yellow leaflets, mp 118°-120°. NMR (in CDCl₃) δ: 2.28 (3H, s), 3.60 (1H, d, J = 14 Hz), 3.83 (1H, d, J = 14 Hz), 4.8 (1H, d, J = 14 Hz), 5.00 (2H, s), 5.10 (2H, s). Mass Spectrum: 479 (M⁺), 388 (M-C₂H₅CH₂F).

cis-5,6-Dihydroxy-2-methylamino-1,2,3,4-tetrahydro-1-napthal enol (27)—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. After about 15 g, hydrogen was absorbed (after ca. 4 hr), the catalyst was filtered off, while the filtrate was dropped into a solution of 10% aqueous H₂SO₄ (190 ml) 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, filtered 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 27-trans fumarate, mp 199° (decomp.). Anal. Calcd. for C₁₅H₁₂O₄N·2CH₂OH·H₂O: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.51; H, 6.72; N, 4.73. NMR (in DMSO-d₆) δ: 2.55 (2H, s), 1.4-3.1 (6H, m), 4.52 (1H, d, J = 9 Hz), 6.88 (2H × 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\textsubscript{11}H\textsubscript{15}O\textsubscript{4}N·HBr: C, 45.58; 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\textsubscript{2}O (6 ml), and the solution was allowed to stand overnight at 5°. Recrystallization of the resulting crystals from a mixture of H\textsubscript{2}O (10 ml) and acetone (100 ml) afforded 315 mg (51%) of 2-cis fumarate, mp 195° (decomp.). Anal. Calcd. for C\textsubscript{15}H\textsubscript{22}O\textsubscript{6}N·1/2C\textsubscript{4}H\textsubscript{6}O\textsubscript{2}: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.20; H, 6.26; N, 5.47. NMR (in DMSO-d\textsubscript{4}) 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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