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Studies on the Structure-Activity Relationship of Adrenergic β-Mimetic Benzylamine Derivatives. IV.[1] Aryl-substituted 1-Aminotetralins and 1-Aminoindans

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The synthesis and adrenergic activity of the stereoisomeric aryl-substituted 1-aminotetralins (**3**, **4**, and **7**) and 1-aminoindans (**5** and **6**), rigid structures related to the benzylamine derivatives (**2**), are presented. Among this series of compounds tested, *trans*-5,6-dihydroxy-1-methylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (**3b**) was the most active tracheal relaxing compound, which was approximately ten times as active as the corresponding *cis* isomer (**4b**) and about two times as active as **2b**. The structure-activity relationship in this series is discussed.

Keywords——1-aminotetralin; 1-aminoindan; trimetoquinol; benzylamine; tracheal relaxing action; positive chronotropic action; β-adrenoceptor agonist; structure-activity relationship

In our earlier work of this series,[3] appropriately substituted benzylamine derivatives (**2**) having a fragmented structure of trimetoquinol (TMQ; **1b**) were found to possess adrenergic β-mimetic activity. Thus, the α-benzyl-3,4-dihydroxybenzylamine system incorporated in both **1** and **2** may be regarded as an essential structural requirement to elicit β-mimetic activity.

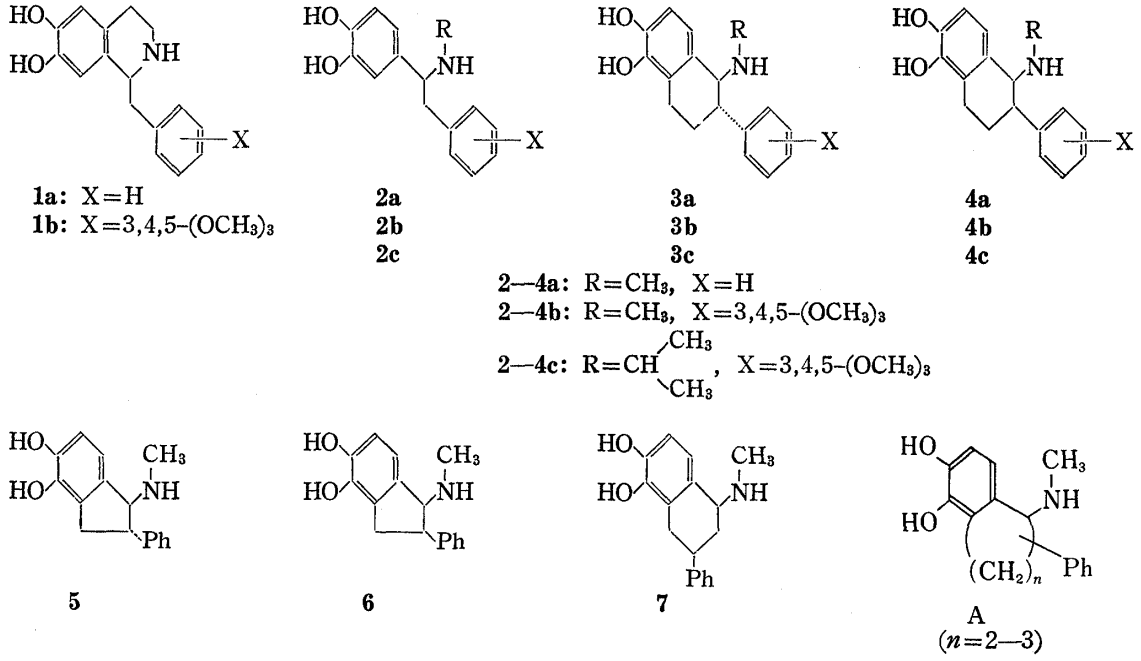

Fig. 1

1) Part III: S. Yamamura, K. Oda, S. Saito, M. Yamazaki, Y. Iwasawa, A. Kiyomoto, and K. Abe, *Heterocycles*, **8**, 211 (1977).
2) Location: *2-2-50, Kawagishi, Toda, Saitama, 335, Japan.*
3) Y. Iwasawa, M. Ohashi, S. Yamamura, S. Saito, and A. Kiyomoto, *Japan. J. Pharmacol.*, **26**, 133 (1976).

In this system, relative spatial arrangement of the catechol, nitrogen, and phenyl groups must play the most important role in receptor association. Conformational mobility of the phenyl group in both **1** and **2**, however, does not allow an insight into this problem. To obtain further information on the steric requirements of these functional groups for β-mimetic activity, therefore, we initiated a study on a series of compounds (A), conformationally constrained analogs of the benzylamine (**2**). By varying ring size (n) as well as the position and stereochemistry of the phenyl group, structure (A) would provide various, rather rigidly

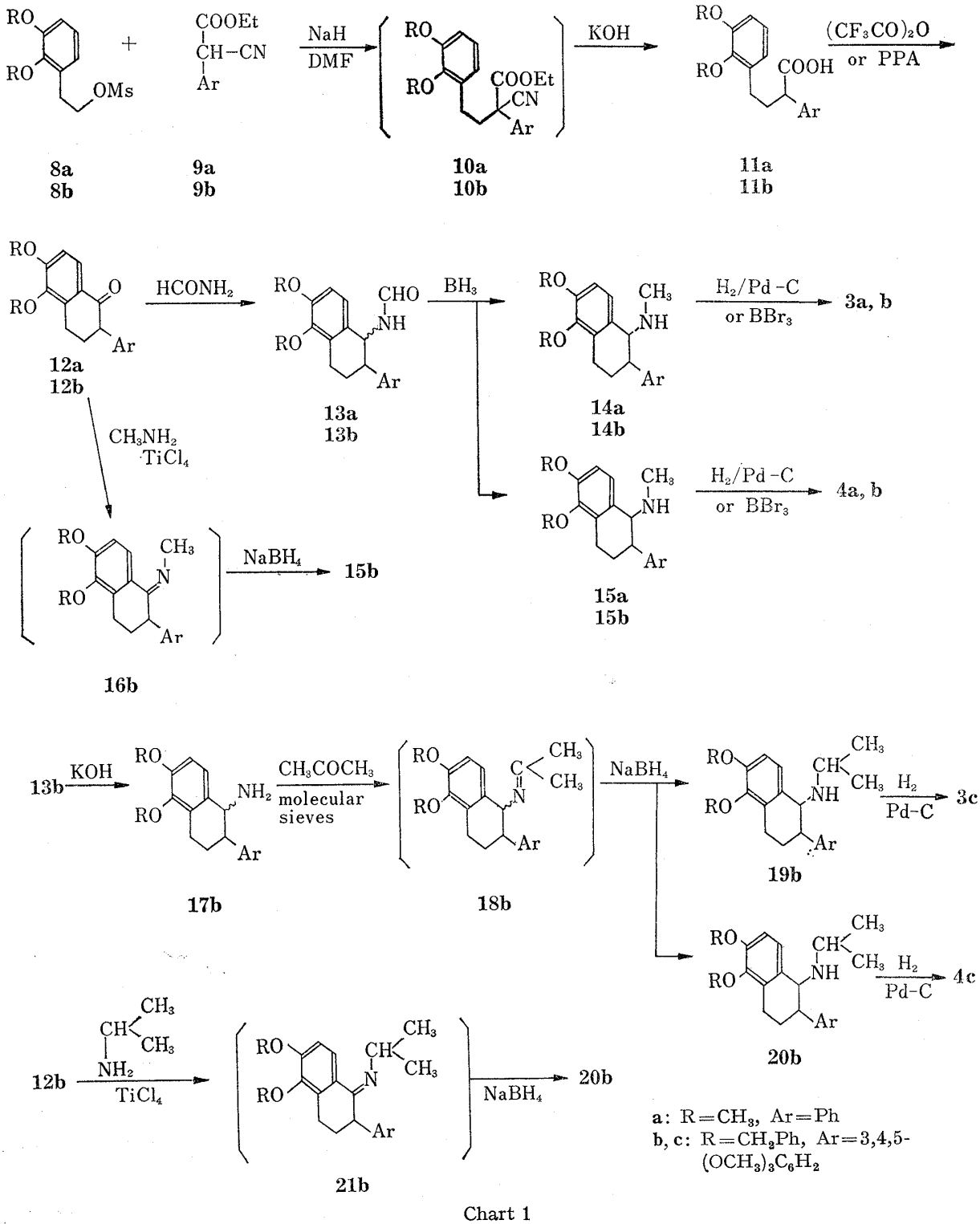

Chart 1

held, spatial orientations of the catechol, nitrogen, and phenyl groups. Described herein are the synthesis and β-mimetic activity of the stereoisomeric aminotetralins (**3**, **4**, and **7**) and aminoindans (**5** and **6**).[4]

1-Alkylamino-2-aryl-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene derivatives (**3a, b, c** and **4a, b, c**) were prepared as illustrated in Chart 1. Condensation of the cyanoesters (**9a** and **9b**) with the mesylates (**8a** and **8b**) in the presence of sodium hydride followed by hydrolysis with KOH in ethylene glycol gave the carboxylic acids (**11a** and **11b**) in 76 and 67.3% yields, respectively. Cyclization of the methoxy acid (**11a**) with PPA gave the tetralone (**12a**) in a 67% yield. Conversion of the corresponding benzyloxy acid (**11b**) into the tetralone (**12b**) was unsuccessful by use of PPA, but was satisfactorily achieved by treatment with trifluoroacetic anhydride[6] in benzene (72% yield). Leuckart reaction of the tetralone (**12a**) with ammonium formate and formamide afforded the amide (**13a**: 80% yield) as a mixture of two stereoisomers. Reduction of this mixture with diborane in THF followed by column chromatography provided the *trans* amine (**14a**: 60%) and the *cis* isomer (**15a**: 37% yield). Similarly, the tetralone (**12b**) was converted to the corresponding *trans* and *cis* amines (**14b** and **15b**). Stereochemical assignments for these isomers were made from the coupling constants of their C_1-protons (**14a, b**: J=8 Hz and **15a, b**: J=4 Hz). The *cis* isomer (**15b**) was alternatively obtained by the method reported by R. Sarges[7] in the stereoselective synthesis of *cis*-1-methylamino-2-phenyl-1,2,3,4-tetrahydronaphthalenes. Thus, reaction of the tetralone (**12b**) with methylamine in the presence of titanium tetrachloride ($TiCl_4$) and subsequent reduction of the resulting imine (**16b**) with $NaBH_4$ gave exclusively **15b** (77% yield).

On the other hand, the N-isopropyl analogs (**19b** and **20b**) were prepared from the primary amine (**17b**, a mixture of stereoisomers) which was obtained in a 81% yield by hydrolysis of

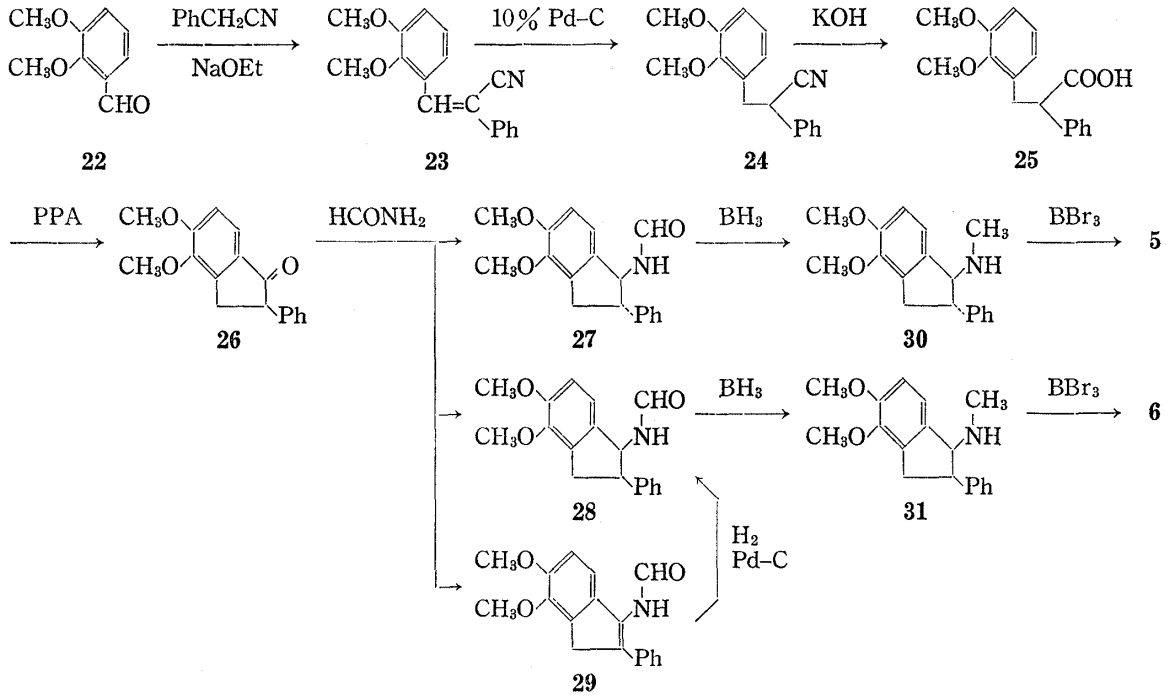

Chart 2

4) A preliminary account of the synthesis and pharmacology of **3b, c** and **4b, c** has been presented. See ref. 5).
5) S. Yamamura, S. Saito, Y. Iwasawa, M. Ohashi, and A. Kiyomoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 3222 (1976).
6) R.J. Ferrier and J.M. Tedder, *J. Chem. Soc.*, **1957**, 1435.
7) R. Sarges, *J. Org. Chem.*, **40**, 1216 (1975).

the amide (**13b**) with KOH in ethylene glycol. Treatment of **17b** with acetone in the presence of molecular sieves (4A) followed by $NaBH_4$ reduction gave, after chromatographic separation, the *trans* amine (**19b**·HCl) and *cis* amine (**20b**·HCl) in 48 and 39% yields, respectively. The latter compound (**20b**) was obtained also from the tetralone (**12b**) in a 86.2% yield by a procedure similar to that described for the *cis* N-methyl relative (**15b**) (isopropylamine–$NaBH_4$).

Hydrogenolysis of **14b**, **15b**, **19b** and **20b** using 10% palladium on charcoal effected removal of the O-benzyl groups and gave the desired catechols (**3b** (94%), **4b** (62.7%), **3c** (75%), and **4c** (50.7% yield)), respectively. O-Demethylation of **14a** and **15a** with boron tribromide afforded the corresponding catechols (**3a** and **4a**) in 81 and 89% yields, respectively.

The synthesis of *trans* and *cis* 1-methylamino-2-phenyl-4,5-dihydroxyindans (**5** and **6**) was carried out essentially in the same manner as described above, the indanone (**26**) serving as a key intermediate (Chart 2). Condensation of the aldehyde (**22**) with benzyl cyanide in the presence of sodium ethoxide gave the acrylonitrile (**23**) in a 92% yield.[8] Reduction of **23** using 10% Pd-C followed by hydrolysis with KOH in ethylene glycol afforded the carboxylic acid (**25**) which cyclized to the indanone (**26**) on treatment with PPA. Leuckart reaction of **26** with ammonium formate and formamide afforded the two stereoisomeric amides (**27**: mp 154.5—155.5°, 35% and **28**: mp 178—182, 31% yields). When this reaction was carried out in the absence of ammonium formate, a small amount of the indene (**29**) was isolated as a by-product. Hydrogenation of **29** using 10% Pd-C gave the indane (**28**), identical with the sample obtained from **26**, *cis* configuration of **28** being thus determined. Reduction of the *trans* and *cis* amides (**27** and **28**) with diborane provided the corresponding amines (**30** (88%) and **31** (94% yield)), respectively. O-Demethylation of **30** and **31** with boron tribromide provided the respective catechols (**5** and **6**) in 86 and 98% yields.

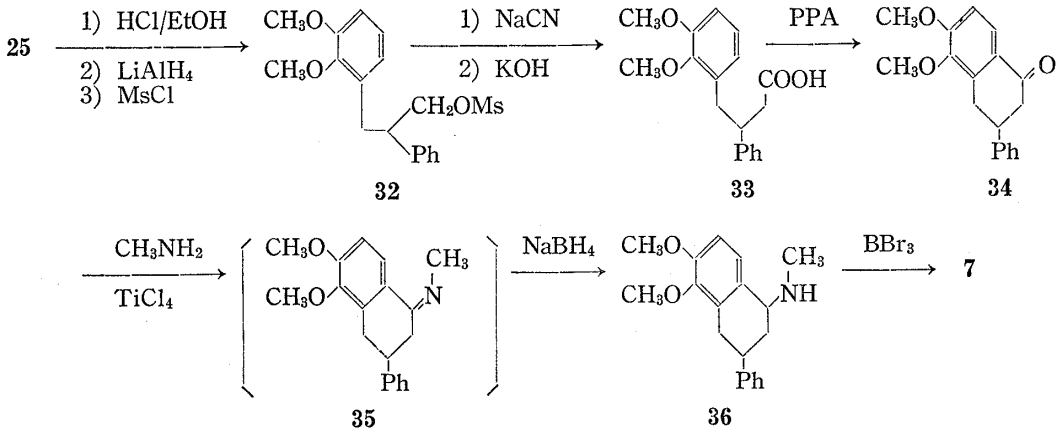

Chart 3

1-Methylamino-3-phenyl-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (**7**), a positional isomer of the phenyl group of **4a**, was prepared from the tetralone (**34**). Preparation of **34** from the carboxylic acid (**25**) was accomplished in a quite straight forward manner as outlined in Chart 3. Treatment of **34** with methylamine and $TiCl_4$ followed by $NaBH_4$ reduction of the resulting imine (**35**) gave the *cis* N-methyl-3-phenylnaphthalene (**36**). *cis* Configuration of **36** was tentatively assigned by analogy with the reported observation in the demethoxy series.[7]

8) T. De. Kiewiet and H. Stephen, *J. Chem. Soc.*, **1931**, 639.

Table I. Tracheal Relaxing Activity

Compd. tested	$pD_2 \pm$S.E.M.[a]	%-relaxation at 3×10^{-4} M
2a	4.14±0.12	73.3±4.6
3a	4.06±0.11	75.0±5.7
4a	<3.5	25.5±6.9
5	<3.5	45.9±4.8
6	<3.5	25.1±3.2
7	<3.5	13.8±0.3
2b	5.98±0.05	
2c	3.96±0.10	60.0±5.2
3b	6.31±0.08	
3c	3.80±0.02	67.0±2.3
4b	5.37±0.16	
4c	3.38±0.07	38.0±3.9

a) Each value represents the mean of more than 6 experiments ±S.E.M. pD_2 values defined as $-\log ED_{50}$.

Pharmacology

Adrenergic β-mimetic activities were determined by the method described in our previous papers.[3,5] Cumulative dose response curves for β_2-activities of the test compounds were studied in the isolated tracheal chains of guinea pigs constracted with histamine (1×10^{-5} g/ml). Table I presents the tracheal relaxing actions of the conformationally constrained analogs (**3**—**7**) related to the benzylamine (**2**). In a series of unsubstituted phenyl derivatives, the order of tracheal relaxing activity observed was **3a**>**5**>**4a**=**6**>**7**. Comparison of the pairs of stereoisomers (**3**—**6**) revealed that the *trans* isomers (**3a** and **5**) were more potent than their *cis* counterparts (**4a** and **6**). Replacement of the phenyl group by a trimethoxyphenyl group in 2-aryl-naphthalene system (**3** and **4**) conferred a remarkable increase in the tracheal relaxing activity in parallel to our previous observation in the benzylamine series (**2a** and **2b**). Thus, the *trans*-1-methylamino-2-trimethoxyphenylnaphthalene (**3b**) was the most active tracheal relaxing compound, which was approximately ten times as active as the corresponding *cis* isomer (**4b**) and about two times as active as **2b**, the most active one in the benzylamine derivatives (Fig. 2). The dose-response curves of these compounds shifted dose-dependently parallel to the right by propranolol.

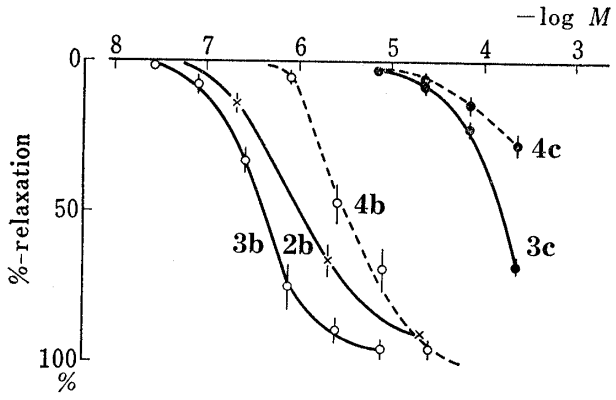

Fig. 2. Dose-response Curves for the Tracheal Relaxing Action

Chemical structures are shown in Fig. 1. Each point represents the mean of more than 6 experiments±S.E.M.

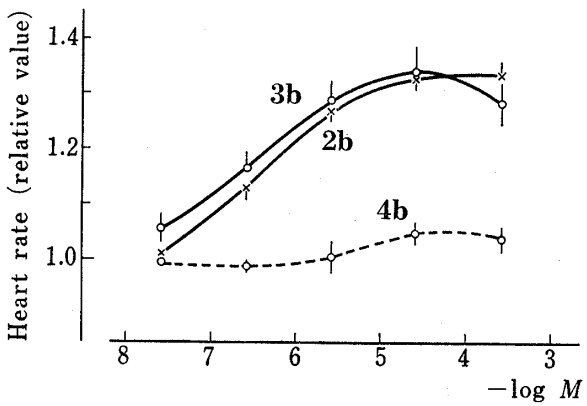

Fig. 3. Dose-response Curves for the Positive Chronotropic Action

The ordinate represents the relative frequency to the initial heart rate prior to the start of the cumulative drug addition. Each point represents the mean of more than 6 experiments ±S.E.M.

With regard to the effect of modifying the substituent on the nitrogen, a change from methyl (**3b** and **4b**) to isopropyl (**3c** and **4c**) caused a marked fall in activity. Similar results have been observed in the benzylamine series (**2b** *vs.* **2c**) previously.

As shown in Fig. 3, the positive chronotropic activity (β_1-mimetic activity) of the *trans*-naphthalene (**3b**) was approximately equal to that of the benzylamine (**2b**), while the *cis*-relative (**4b**) was almost inactive up to 3×10^{-4} mol concentration. The *cis*-naphthalene (**4b**) was thus found to possess high selectivity for β_2-adrenoceptor compared with the corresponding **3b** and **2b**.

In conclusion, by transformation of the benzylamine derivatives (**2**) into more rigid structures such as **3**, **4**, **5**, **6**, and **7**, it was revealed that the β_2-mimetic activity of α-benzyl-3,4-dihydroxy-benzylamine system is quite susceptible to a small change in the spatial arrangement of their catechol, nitrogen, and phenyl groups. In these conformationally constrained structures, the *trans*-aminotetralin derivative (**3b**) was found to possess more potent β_2-activity than its original benzylamine (**2b**).

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. IR spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were determined on a Model JEOL ME-60 instrument in $CDCl_3$ (containing tetramethylsilane at δ 0.00 as an internal standard), unless otherwise specified. Coupling constants (J) are given in Hz and the following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra (MS) were measured on a Hitachi RMS-4 mass spectrometer. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out *in vacuo*.

2,3-Dibenzyloxyphenethyl Methanesulfonate (8b)——A mixture of 2,3-dimethoxyphenylacetic acid[9] (50 g) and 47% HBr (500 g) was refluxed for 4 hr and evaporated to give crude 2,3-dihydroxyphenylacetic acid[10] as a crystalline residue. This residue was esterified by refluxing with HCl–EtOH for 2 hr and evaporated to give crude ethyl 2,3-dihydroxyphenylacetate. A mixture of this ester, NaI (0.5 g), benzyl chloride (129 g), K_2CO_3 (141 g), and EtOH (400 ml) was refluxed under stirring for 24 hr. The inorganic materials were filtered off and the filtrate was evaporated. The residue was dissolved in AcOEt and washed with H_2O. Evaporation of the dried AcOEt gave crude ethyl 2,3-dibenzyloxyphenylacetate as an oil. A solution of this oil in ether (100 ml) was added to a mixture of $LiAlH_4$ (19.4 g) and ether (300 ml) at 5° and stirring was continued at room temperature for 3 hr. The mixture was decomposed with H_2O (60 ml) and the inorganic material was filtered off. The filtrate was washed with 10% NaOH and H_2O, dried, and evaporated to give 82.5 g (97%) of 2,3-dibenzyloxyphenethyl alcohol as needles, mp 67—68° (ether–petroleum ether). NMR: 1.85 (1H, t, J=7, O$\underline{H}$), 2.85 (2H, t, J=7, Ar–CH_2–), 3.80 (2H, q, J=7, –C$\underline{H}_2$OH), 5.08, 5.14 (4H, each s, 2×PhCH_2O), 6.7—7.2 (3H, m, Ar–H), 7.2—7.65 (10H, m, 2×C$_6\underline{H}_5$CH_2). *Anal.* Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63. Found: C, 78.62; H, 6.65.

To a stirred solution of this carbinol (37 g) in pyridine (130 ml) was added mesyl chloride (19 g) at −10° for 1 hr. Stirring was continued overnight at room temperature and the mixture was poured onto ice-water to give a precipitate. This precipitate was taken in $CHCl_3$, washed with H_2O, 10% HCl, and H_2O, successively. Evaporation of the dried $CHCl_3$ gave 45 g (99.2%) of **8b** as colorless granules, mp 75—77°. NMR: 2.74 (3H, s, SO_2CH_3), 2.99 (2H, t, J=7, Ar–C$\underline{H}_2$CH_2–), 4.33 (2H, t, J=7, ArCH_2C$\underline{H}_2$O), 5.09, 5.14 (4H, each s, 2×PhCH_2O), 6.6—7.1 (3H, m, Ar–H), 7.2—7.5 (10H, m, Ar–H). *Anal.* Calcd. for $C_{23}H_{24}O_5S$: C, 66.97; H, 5.86; S, 7.77. Found: C, 67.06; H, 5.98; S, 7.69.

2,3-Dimethoxyphenethyl Methanesulfonate (8a)——To a stirred solution of 2,3-dimethoxyphenethyl alcohol[11] (7.2 g) in pyridine (30 ml) was added mesyl chloride (4.53 g) at −10°. The mixture was worked up in the same manner as that described above to give 10.5 g (82.7%) of **8a** as an oil. NMR: 2.74 (3H, s, SO_2CH_3), 3.07 (2H, t, J=7, –C$\underline{H}_2$CH_2O), 3.80 (6H, s, 2×OCH_3), 4.41 (2H, t, J=7, –CH_2C$\underline{H}_2$O), 6.7—7.2 (3H, m, Ar–H).

Ethyl 3,4,5-Trimethoxyphenylcyanoacetate (9b)——To a mixture of 3,4,5-trimethoxybenzyl cyanide[12] (41.4 g) and diethyl carbonate (118 g) was added a solution of sodium ethoxide (prepared from Na (5.5 g)) in EtOH (120 ml) at 100° under stirring for 7 hr and stirring was continued for additional 14 hr.[13] The

9) C. Späth and E. Mosetting, *Ann.*, **433**, 146 (1923).
10) W. Mosimann and J. Tambor, *Chem. Ber.*, **46**, 1260 (1916).
11) S. Sugasawa and H. Shigehara, *Chem. Ber.*, **74**, 459 (1941).
12) W. Baker and R. Robinson, *J. Chem. Soc.*, **1929**, 152.
13) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

mixture was poured onto ice-water, acidified with acetic acid, and extracted with ether. The extracts were washed with H_2O, dried, and evaporated. Distillation of the residue gave 45.5 g (81.5%) of **9b**, bp 180° (0.5 mmHg). IR ν_{max}^{liquid} cm^{-1}: 2250 (CN), 1740 (CO). MS *m/e*: 279 (M^+). NMR: 1.31 (3H, t, $J=7$, OCH_2CH_3), 3.86 (3H, s, OCH_3), 3.90 (6H, s, $2\times OCH_3$), 4.28 (2H, q, $J=7$, OCH_2CH_3), 4.68 (1H, s, –CHCN), 6.71 (2H, s, Ar–H).

γ-(2,3-Dibenzyloxyphenyl)-α-(3,4,5-trimethoxyphenyl)butyric Acid (11b)——To a mixture of 69% NaH (4.2 g) in DMF (60 ml) was added a solution of **9b** (27.9 g) in DMF (60 ml) under ice cooling and the mixture was stirred for 40 min. A solution of **8b** (41.3 g) in DMF (60 ml) was added to the reaction mixture at 20° during 1 hr and stirring was continued at 120° for 32 hr. The mixture was evaporated, diluted with ice-water, and extracted with ether. The extracts were washed with water and evaporated to afford an oily residue (**10b**). A mixture of this residue, KOH (45 g), ethylene glycol (450 ml) and water (45 ml) was refluxed for 27 hr. The mixture was poured onto ice-water, washed with ether, acidified with c.HCl, and then extracted with $CHCl_3$. Evaporation of the extracts gave 65 g of an oil which was chromatographed over silica gel. Elution with $CHCl_3$–MeOH (100: 3) gave, after crystallization from isopropylether, 36.5 g (67.3%) of colorless crystals (**11b**), mp 72—74°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32. Found: C, 72.88; H, 6.38.

5,6-Dibenzyloxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydro-1(2H)-naphthalenone (12b)——A mixture of **11b** (10 g) and trifluoroacetic anhydride (20 ml) in C_6H_6 (150 ml) was refluxed for 3 hr under stirring. Evaporation of the mixture gave, after recrystallization from AcOEt–isopropylether, 7.0 g (72%) of **12b** as colorless needles, mp 158—160°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO). NMR: 3.81 (6H, s, $2\times OCH_3$), 3.84 (3H, s, OCH_3), 5.06, 5.23 (4H, each s, $2\times PhCH_2O$–), 6.40 (2H, s, Ar–H), 7.01 (1H, d, $J=9$, Ar–H), 7.37, 7.44 (10H, each s, $2\times C_6H_5$), 7.92 (1H, d, $J=9$, Ar–H). *Anal.* Calcd. for $C_{33}H_{32}O_6$: C, 75.55; H, 6.15. Found: C, 75.50; H, 6.32. The mother liquor (AcOEt–isopropylether) was evaporated and recrystallized from isopropylether to afford 1.5 g (9%) of 5,6-dibenzyloxy-1-trifluoroacetoxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphtalene as colorless needles, mp 118—119°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800 ($COCF_3$). MS *m/e*: 620 (M^+). *Anal.* Calcd. for $C_{35}H_{31}F_3O_7$: C, 67.73; H, 5.04; F, 9.18. Found: C, 67.91; H, 5.03; F, 8.90.

5,6-Dimethoxy-2-phenyl-3,4-dihydro-1(2H)-naphthalenone (12a)——Crude oily γ-(2,3-dimethoxyphenyl)-α-phenyl butyric acid (**11a**) (7.0 g), which was obtained from **8a** (8.0 g) and **9a** (5.8 g) in the same manner described above, was mixed with PPA (130 g) and heated at 90° for 20 min with stirring. The mixture was poured onto ice-water and extracted with ether. The extracts were successively washed with aq. $NaHCO_3$ and H_2O. Evaporation of the dried extracts gave, after recrystallization from ether, 4.1 g (67%) of colorless prisms (**12a**), mp 146—148°. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.68; H, 6.46.

5,6-Dibenzyloxy-1-formylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (13b)——A mixture of **12b** (1 g) and ammonium formate (0.33 g) in formamide (20 ml) was stirred at 170° for 6 hr. The mixture was poured onto ice-water and extracted with $CHCl_3$. Evaporation of the dried extracts gave, after recrystallization from EtOH–isopropylether, 0.88 g (83%) of colorless needles (**13b**) as a mixture of two stereoisomers, mp 170—173°. IR ν_{max}^{Nujol} cm^{-1}: 1650 (NHCO). *Anal.* Calcd. for $C_{34}H_{35}NO_6$: C, 73.76; H, 6.37; N, 2.53. Found: C, 73.76; H, 6.42; N, 2.43.

1-Formylamino-5,6-dimethoxy-2-phenyl-1,2,3,4-tetrahydronaphthalene (13a)——A mixture of **12a** (2.82 g) and ammonium formate (12.6 g) in formamide (25 ml) was stirred at 180° for 1.5 hr. The mixture was poured onto ice-water and extracted with $CHCl_3$. Evaporation of the dried extracts afforded a residue which was chromatographed over silica gel (200 g) in $CHCl_3$. The first part of the eluate gave 0.2 g (8%) of 5,6-dimethoxy-2-phenyl-3,4-dihydronaphthalene, colorless plates from EtOH, mp 126—128°. MS *m/e*: 266 (M^+). NMR: 2.4—3.3 (4H, m), 3.86, 3.88 (6H, each s, $2\times OCH_3$), 6.88 (1H, d, $J=8$, Ar–H), 6.90 (1H, d, $J=8$, Ar–H), 6.80 (1H, d, $J=2$, –CH=C–Ph), 7.2—7.7 (5H, m, $-C_6H_5$). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.04; H, 6.96. The following elution gave a mixture of two stereoisomers (**13a**) (2.49 g, 80%) as colorless needles (from EtOH), mp 174—177°. MS *m/e*: 311 (M^+). *Anal.* Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.26; H, 6.95; N, 4.31.

***cis* and *trans*-5,6-Dibenzyloxy-1-methylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (15b and 14b)**——A mixture of **12b** (4 g) and formamide (60 ml) was stirred at 170° for 6 hr. The mixture was worked up in the same manner as that described above to give crude **13b**. To a mixture of this product and $NaBH_4$ (5.8 g) in THF (280 ml) was added boron trifluoride etherate (21.6 g) at 5° and stirred at room temperature overnight. The mixture was decomposed with ether containing H_2O and evaporated. The residue was treated with HCl–MeOH, diluted with $CHCl_3$ and H_2O, and basified with aq. NaOH. The organic layer was washed with H_2O and evaporated. The residue was chromatographed on silica gel (120 g) in $CHCl_3$. The earlier part of the eluate gave 1.4 g (34%) of the *cis* isomer (**15b**), mp 118—119°. The hydrochloride was recrystallized from AcOEt–isopropylether to give **15b**·HCl as colorless needles, mp 195—197°. NMR (free base in $CDCl_3+D_2O$, 100 MHz): 2.47 (3H, s, NCH_3), 3.66 (1H, d, $J=4$, N–CH–), 3.87 (6H, s, $2\times OCH_3$), 3.89 (3H, s, OCH_3), 5.02, 5.14 (2H, each d, $J=11$, $-CH_2Ph$), 5.15 (2H, s, CH_2Ph), 6.54 (2H, s, Ar–H), 6.85 (1H, d, $J=8$, Ar–H), 6.98 (1H, d, $J=8$, Ar–H), 7.2—7.5 (10H, m, Ar–H). *Anal.* Calcd. for $C_{34}H_{37}NO_5$·HCl: C, 70.88; H, 6.65; N, 2.43; Cl, 6.15. Found: C, 70.72; H, 6.62; N, 2.44; Cl, 6.33. The following elution gave, after recrystallization from EtOH, 2.17 g (53%) of the *trans* counterpart (**14b**) as needles, mp 132—134°, (**14b**·HCl: mp 175—177° from EtOH). NMR (free base in $CDCl_3$, 100 MHz): 2.30 (3H, s, NCH_3), 3.83 (6H,

s, 2×OCH_3), 3.87 (3H, s, OCH_3), 4.02 (1H, d, J=8, N–CH–CH–Ar), 5.04, 5.16 (4H, each s, 2×$PhCH_2O$), 6.42 (2H, s, Ar–H), 6.92 (1H, d, J=8, Ar–H), 7.2—7.6 (11H, m, Ar–H and 2×C_6H_5). *Anal.* Calcd. for $C_{34}H_{37}NO_5$: C, 75.67; H, 6.91; N, 2.60. Found: C, 75.56; H, 6.99; N, 2.52.

***cis* and *trans*-5,6-Dimethoxy-1-methylamino-2-phenyl-1,2,3,4-tetrahydronaphthalene (14a and 15a) Hydrochlorides**——To a solution of a mixture of two stereoisomers (**13a**) (1.54 g) in THF (60 ml) was added a solution of diborane in THF (10% solution, 10 ml). The mixture was stirred at room temperature for 2 hr and then under refluxing for 2 hr. Evaporation of the solvent gave the residue which was treated with HCl–MeOH and the solvent was removed. The residue was taken in H_2O, washed with ether, basified with 10% NaOH, and extracted with AcOEt. Evaporation of the dried extracts gave a mixture of two stereoisomers (**14a** and **15a**) as an oil which was purified through preparative TLC [silica gel, developed by $CHCl_3$–MeOH (20: 1)]. The *cis* isomer (**15a**) (550 mg, 37%) obtained from the upper fraction was converted to the hydrochloride. Needles from MeOH–ether, mp 214—217°. NMR (free base in $CDCl_3$, 100 MHz): 2.18 (3H, s, NCH_3), 3.66 (1H, d, J=4, N–CH–CH–Ph), 3.84, 3.88 (6H, each s, 2×OCH_3), 6.78 (1H, d, J=8, Ar–H), 6.98 (1H, d, J=8, Ar–H), 7.30 (5H, s, C_6H_5–). *Anal.* Calcd. for $C_{19}H_{23}NO_2$·HCl: C, 68.35; H, 7.25; N, 4.20; Cl, 10.62. Found: C, 68.47; H, 7.45; N, 4.02; Cl, 10.67. The *trans* counterpart (**14a**) (890 mg, 60%) obtained from the lower fraction was converted to the hydrochloride. Needles from MeOH–ether, mp 174—176°. NMR (free base in $CDCl_3$, 100 MHz): 2.25 (3H, s, N–CH_3), 3.81, 3.88 (6H, each s, 2×OCH_3), 4.01 (1H, d, J=8, N–CH–CH–Ph), 6.80 (1H, d, J=8, Ar–H). *Anal.* Calcd. for $C_{19}H_{23}NO_2$·HCl: C, 68.35; H, 7.25; N, 4.20; Cl, 10.62. Found: C, 68.28; H, 7.53; N, 4.03; Cl, 10.41.

***cis*-5,6-Dibenzyloxy-1-methylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (15b) Hydrochloride**——To a solution of the tetralone (**12b**) (2 g) and methylamine (1.18 g) in C_6H_6 (90 ml) was added a solution of $TiCl_4$ (720 mg) in C_6H_6 (10 ml) under ice-cooling during 1 hr. The mixture was stirred for 3 days and filtered from inorganic material. Evaporation of the filtrate left crude imine (**14b**) as an oil which was taken in MeOH (150 ml) and treated with $NaBH_4$ (430 mg) for 4 hr. The mixture was decomposed by H_2O, concentrated, and extracted with ether. Evaporation of the dried extracts left a crystalline residue which was converted to the hydrochloride. Recrystallization from AcOEt–isopropylether gave 1.7 g (77.4%) of *cis* isomer (**15b**), mp 195—197°. This compound was identified with the sample (from the upper fraction on preparative TLC) previously obtained from the amide (**13b**) (IR, mixed mp, and TLC).

1-Amino-5,6-dibenzyloxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (17b)——A mixture of **12b** (12 g) and ammonium formate (4 g) in formamide (120 ml) was stirred at 170—175° for 6 hr. The mixture was worked up in the same manner as that described above to give 15 g of residue (**13b**). A mixture of this residue, KOH (24 g), H_2O (50 ml) and ethylene glycol (150 ml) was refluxed for 22 hr. The mixture was poured onto ice-water and extracted with $CHCl_3$. Evaporation of the dried extracts left a crystalline residue which was recrystallized from EtOH to give 9.5 g (79%) of **17b** as a mixture of two stereoisomers. Plates from EtOH, mp 139—141°. *Anal.* Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.43; H, 6.86; N, 2.66.

***cis* and *trans*-5,6-Dibenzyloxy-1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (20b and 19b) Hydrochlorides**——A mixture of **17b** (1 g), acetone (100 ml) and molecular sieves (10 g) was stirred at room temperature for 3 days and filtered from inorganic material. Evaporation of the filtrate left the crude imine which was taken in MeOH (50 ml) and treated with $NaBH_4$ (360 mg) for 3 hr. The mixture was decomposed by H_2O, concentrated, and extracted with $CHCl_3$. Evaporation of the dried extracts gave a mixture of two stereoisomers (**20b** and **19b**) as an oil which was purified through preparative TLC [silica gel, developed by $CHCl_3$–MeOH (20: 1)]. Upper fraction gave the *cis* isomer (**20b**) as an oil which was converted to the hydrochloride. Recrystallization from AcOEt–isopropylether gave 450 mg (39%) of the *cis* isomer (**20b**·HCl) as needles, mp 202—204°. NMR (**20b**·HCl in $CDCl_3$, 100 MHz): 0.97, 1.28 (6H, each d, J=7, $CH(CH_3)_2$), 3.88 (3H, s, OCH_3), 3.97 (6H, s, 2×OCH_3), *ca.* 4.45 (1H, broad s, –CH–N), 4.96, 5.16 (2H, each d, J=12, $PhCH_2$–), 5.18 (2H, s, $PhCH_2$), 6.82 (2H, s, Ar–H), 6.98 (1H, d, J=8, Ar–H), 7.21 (1H, d, J=8, Ar–H), 7.25—7.6 (10H, m, 2×C_6H_5). *Anal.* Calcd. for $C_{36}H_{41}NO_5$·HCl: C, 71.56; H, 7.01; N, 2.32; Cl, 5.87. Found: C, 71.55; H, 7.14; N, 2.27; Cl, 6.00. Lower fraction gave the *trans* isomer **19b** as an oil which was converted to the hydrochloride. Recrystallization from MeOH–ether gave 550 mg (48%) of the *trans* isomer (**19b**·HCl) as colorless crystals, mp 142—144°. NMR (**19b**·HCl in $CDCl_3$, 100 MHz) 1.31, 1.33 (6H, each d, J=7, $CH(CH_3)_2$), 3.75 (6H, s, 2×OCH_3), 3.83 (3H, s, OCH_3), *ca.* 4.50 (1H, broad s, –CH–N), 5.02, 5.13 (4H, each s, 2×$PhCH_2$), 6.44 (2H, s, Ar–H), 6.99 (1H, d, J=8, Ar–H), 7.2—7.6 (11H, m, Ar–H). *Anal.* Calcd. for $C_{36}H_{41}NO_5$·HCl: C, 71.56; H, 7.01; N, 2.32; Cl, 5.87. Found: C, 71.41; H, 7.14; N, 2.36; Cl, 5.85.

***cis*-5,6-Dibenzyloxy-1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (20b) Hydrochloride**——To a stirred solution of the tetralone (**12b**) (1 g) and isopropylamine (4 ml) in C_6H_6 (10 ml) was added a solution of $TiCl_4$ (362 mg) in C_6H_6 (10 ml). After stirring for 4 days, the mixture was filtered from inorganic material and evaporated. The residue was taken in MeOH and reduced with $NaBH_4$ in the same manner as that described for the *cis* N-methyl relative (**17b**). Usual work up gave an oil which was converted to the hydrochloride and recrystallized from AcOEt to give 990 mg (86%) of the *cis* isomer (**20b**·HCl), needles, mp 202—204°. This compound was identified with the sample (higher fraction on preparative TLC) previously obtained from the amine (**17b**) (IR, mixed mp, and TLC).

***trans*-5,6-Dihydroxy-1-methylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (3b) Hydrochloride**——A mixture of **14b** (0.9 g), $CHCl_3$ (20 ml) and MeOH (50 ml) was hydrogenated over 10% Pd–C (0.4 g) at room temperature. The catalyst was filtered off and the filtrate was treated with HCl/MeOH, and evaporated. Recrystallization from MeOH–ether gave 620 mg (94%) of colorless prisms (**3b**·HCl), mp 173—176°. NMR (**3b**·HCl in d_6-DMSO): 2.57 (3H, s, N–CH_3), 3.63 (3H, s, OCH_3), 3.69 (6H, s, $2\times OCH_3$), *ca.* 4.65 (1H, m, N–CH–CH–Ar), 6.55 (2H, s, Ar–H), 6.80 (1H, d, $J=8$, Ar–H), 7.06 (1H, d, $J=8$, Ar–H), 8.58, 9.61 (4H, each s, $2\times$OH and NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{20}H_{25}NO_5\cdot HCl$: C, 60.68; H, 6.62; N, 3.54; Cl, 8.96. Found: C, 60.43; H, 6.57; N, 3.49; Cl, 8.85.

***cis*-5,6-Dihydroxy-1-methylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (4b) Hydrochloride**——Hydrogenation of **15b** (1.0 g) in the same manner as that described above gave, after recrystallization from MeOH–ether, 460 mg (63%) of colorless needles (**4b**·HCl), mp 172—174°. NMR (**4b**·HCl in d_6-DMSO): 2.25 (3H, s, N–CH_3), 6.81 (4H, s, Ar–H), 8.63, 9.65 (4H, each s, $2\times$OH and NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{20}H_{25}NO_5\cdot HCl\cdot 1/2H_2O$: C, 59.33; H, 6.72; N, 3.46; Cl, 8.76. Found: C, 59.14; H, 6.75; N, 3.40; Cl, 9.14.

***trans*-5,6-Dihydroxy-1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (3c) Hydrochloride**——Similar hydrogenation of **19b**·HCl (450 mg) gave, after recrystallization from MeOH–ether, 240 mg (75%) of colorless prisms, mp 140—143°. *Anal.* Calcd. for $C_{22}H_{29}NO_5\cdot HCl\cdot 1/4H_2O$: C, 61.67; H, 7.18; N, 3.27; Cl, 8.28. Found: C, 61.68; H, 7.17; N, 3.37; Cl, 8.51.

***cis*-5,6-Dihydroxy-1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (4c) Hydrochloride**——Similar hydrogenation of **20b**·HCl (0.9 g) gave, after recrystallization from MeOH–ether, 320 mg (50.7%) of colorless needles, mp 114—119°. *Anal.* Calcd. for $C_{22}H_{29}NO_5\cdot HCl$: C, 62.33; H, 7.13; N, 3.30; Cl, 8.36. Found: C, 62.02; H, 7.25; N, 3.19; Cl, 8.16.

***trans*-5,6-Dihydroxy-1-methylamino-2-phenyl-1,2,3,4-tetrahydronaphthalene (3a) Hydrobromide**——To a mixture of **14a**·HCl (0.63 g) and CH_2Cl_2 (10 ml) was added boron tribromide (0.9 ml) at −78° under N_2. The mixture was stirred at −78° for 2 hr and at room temperature for an additional 2 hr. The mixture was decomposed by addition of MeOH and evaporated. Recrystallization from MeOH–ether gave 590 mg (81%) of the *trans* isomer (**3a**·HBr) as leaflets, mp 104—106°. NMR (**3a**·HBr in trifluoroacetic acid): 2.85 (3H, s, NCH_3), 4.10 (3H, s, CH_3OH), 5.0—5.3 (1H, m, >CH–NH–), 7.14 (2H, s, Ar–H), 7.40 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{17}H_{19}NO_2\cdot HBr\cdot CH_3OH$: C, 56.55; H, 6.33; N, 3.66. Found: C, 56.36; H, 6.41; N, 3.65.

***cis*-5,6-Dihydroxy-1-methylamino-2-phenyl-1,2,3,4-tetrahydronaphthalene (4a) Hydrobromide**——The *cis* isomer (**15a**·HCl) (0.65 g) was demethylated as described above to give 660 mg (89%) of **4a**·HBr. Colorless prisms from MeOH–ether, mp 123—126°. NMR (**4a**·HBr in trifluoroacetic acid): 2.75 (3H, s, NCH_3), 4.10 (3H, s, CH_3OH), 4.40—4.70 (1H, m, >CH–N), 7.05 (2H, s, Ar–H), 7.50 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{17}H_{19}NO_2\cdot HBr\cdot CH_3OH$: C, 56.55; H, 6.33; N, 3.66; Br, 20.90. Found: C, 56.59; H, 6.27; N, 3.61; Br, 20.78.

3-(2,3-Dimethoxyphenyl)-2-phenylacrylonitrile (23)——To a solution of 2,3-dimethoxybenzaldehyde (5.0 g) and benzyl cyanide (3.5 g) in EtOH (30 ml) was added a solution of sodium ethoxide (prepared from Na (0.7 g)) in EtOH (10 ml) and the mixture was stirred at room temperature for 1 hr. Filtration and recrystallization from EtOH gave 7.30 g (92%) of needles (**23**), mp 83—85°. IR ν_{max}^{Nujol} cm^{-1}: 2220 (CN). MS *m/e*: 265 (M^+). NMR: 3.88 (6H, s, $2\times OCH_3$) 7.0—7.9 (8H, m, Ar–H), 8.00 (1H, s, –CH=C–CN). *Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.74; H, 5.87; N, 5.32.

3-(2,3-Dimethoxyphenyl)-2-phenylpropionitrile (24)——A solution of **23** (75.1 g) in EtOH (1.5 l) was hydrogenated over 10% Pd–C (7.5 g) at room temperature. The catalyst was filtered off and the filtrate was evaporated to give crude **24** (75.5 g), which was used to the next step.

3-(2,3-Dimethoxyphenyl)-2-phenylpropionic Acid (25)——A mixture of the nitrile (**24**) (75.5 g), KOH (27.9 g), and H_2O (50 ml) in ethylene glycol (1 l) was heated at 120° for 39 hr. The mixture was diluted with H_2O (1.5 l), extracted with $CHCl_3$, and washed with H_2O. Evaporation of the dried extracts gave, after recrystallization from isopropyl alcohol, 5.8 g (7%) of 3-(2,3-dimethoxyphenyl)-2-phenylpropionamide as prisms, mp 142.0—143.5°. MS *m/e*: 285 (M^+). NMR (d_6-DMSO): 2.8—3.5 (3H, m), 3.71, 3.76 (6H, each s, $2\times OCH_3$), 6.6—7.0 (4H, m), 7.2—7.7 (6H, m). *Anal.* Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.61; H, 7.00; N, 4.86. The aqueous layer was acidified with 10% HCl, extracted with ether, and washed with H_2O. Evaporation of the dried extracts gave 66.5 g (82%) of **25**. Prisms from isopropylether, mp 124—126°. IR ν_{max}^{Nujol} cm^{-1}: 1700. *Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.40; H, 6.26.

4,5-Dimethoxy-2-phenyl-1-indanone (26)——A mixture of **25** (18.9 g) and PPA (200 g) was stirred at 75—80° for 2 hr. The mixture was poured onto ice-water and extracted with AcOEt. The extracts were successively washed with aq. $NaHCO_3$ and H_2O. After evaporation of the dried extracts, the residue was chromatographed over silica gel (300 g). Elution with benzene–AcOEt (20:1) gave, after crystallization from isopropylether, 13.5 g (76%) of needles (**26**), mp 75—78°. IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO). MS *m/e*: 268 (M^+). NMR: 3.0—3.9 (3H, m), 3.95 (6H, s, $2\times OCH_3$), 7.05 (1H, d, $J=9$, Ar–H), 7.30 (5H, s, Ar–H), 7.63 (1H, d, $J=9$, Ar–H). *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.11; H, 6.15.

***cis* and *trans*-1-Formylamino-4,5-dimethoxy-2-phenylindan (28 and 27)**——A): A mixture of **26** (7.8 g) ammonium formate (41.7 g) and formamide (35 ml) was stirred at 180° for 17 hr. The mixture was poured onto ice-water and extracted with AcOEt. The insoluble substance was collected by filtration and recrystallized from EtOH to give 2.4 g of the *cis* isomer (**28**) as prisms, mp 178—182°. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1650 (CO). MS *m/e*: 297 (M^+). NMR ($CDCl_3$+d_6-DMSO): 3.24 (2H, s, $-CH_2-$), 3.87 (6H, s, $2\times OCH_3$), 3.8—4.1 (1H, m, -CH-), 5.6—5.9 (1H, m, -CH-N), 6.9—7.8 (8H, m), 7.95 (1H, broad s). *Anal.* Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.37; H, 6.56; N, 4.65. The organic layer (AcOEt) was washed with aq. $NaHCO_3$ and H_2O. Evaporation of the extracts gave, after recrystallization from MeOH, 1.4 g of the *trans* counterpart (**27**) as needles, mp 154.5—155.5°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1660. MS *m/e*: 297 (M^+). NMR: 2.8—3.8 (3H, m, $-CH_2-CH-$), 3.87 (6H, s, $2\times OCH_3$), 5.4—5.8 (1H, m, -CH-N), 6.2—6.6 (1H, m), 6.8—7.6 (7H, m), 8.27 (1H, broad s). *Anal.* Calcd. for $C_{18}H_{17}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.69; H, 6.61; N, 4.55. After evaporation of the mother liquor (EtOH and MeOH), the residue was chromatographed over silica gel (120 g) and eluted with $CHCl_3$. Evaporation of the eluate gave the additional *cis* isomer (**28**) (0.3 g, total yield 31%) and *trans* counterpart (**27**) (1.6 g, total yield 35%).

B): When the reaction was carried out in the absence of ammonium formate, a very small amount of the indene (**29**) was isolated as a by-product. Pale yellow granules from EtOH, mp 204.0—205.5°. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1650 (CO), 1630 (C=C). MS *m/e*: 295 (M^+). NMR: 3.79 (2H, s, $-CH_2-$), 3.86, 3.92 (6H, each s, $2\times OCH_3$), 7.0—7.9 (7H, m), 8.4—8.5 (1H, m). *Anal.* Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.93; H, 6.16; N, 4.80.

A solution of the indene (**29**) (59 mg) in EtOH (10 ml) was hydrogenated over 10% Pd-C (30 mg) under ordinary temperature and pressure. The catalyst was filtered off and the filtrate was evaporated to give 30 mg of the *cis* isomer (**28**) as prisms, mp 178—182°, identical with the sample previously obtained from **26** (IR, mixed mp, and TLC).

***trans*-4,5-Dimethoxy-1-methylamino-2-phenylindan (30)**——To a solution of **27** (2.4 g) in THF (100 ml) was added 16 ml of 1 M diborane under cooling. The mixture was stirred at room temperature for 2 hr and under refluxing for further 1.5 hr. The mixture was decomposed by addition of 34% HCl–MeOH (12 ml), concentrated, diluted with H_2O, and washed with AcOEt. The aqueous layer was basified with K_2CO_3 and extracted with AcOEt. Evaporation of the dried extracts gave, after recrystallization from isopropylether, 2.0 g (88%) of granules (**30**), mp 94—96°. MS *m/e*: 283 (M^+). NMR: 1.60 (1H, s, NH), 2.47 (3H, s, $N-CH_3$), 3.0—3.7 (3H, m, $-CH_2-CH-$), 3.90 (6H, s, $2\times OCH_3$), 4.31 (1H, d, J=6, -CH-N), 6.87 (1H, d, J=7, Ar-H), 7.07 (1H, d, J=7, Ar-H), 7.29 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.44; H, 7.50; N, 4.75.

***cis*-4,5-Dimethoxy-1-methylamino-2-phenylindan (31)**——The *cis* isomer (**28**) (2.0 g) was reduced with diborane as described above to afford, after recrystallization from isopropylether, 1.8 g (94%) of pillars (**31**), mp 85—87°. MS *m/e*: 283 (M^+). NMR: 1.24 (1H, s, NH), 2.28 (3H, s, $N-CH_3$), 3.2—3.8 (3H, m, $-CH_2-CH-$), 3.87 (6H, s, $2\times OCH_3$), 4.15 (1H, d, J=7, -CH-N), 6.79 (1H, d, J=8, Ar-H), 7.06 (1H, d, J=8, Ar-H), 7.28 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.56; H, 7.68; N, 4.90.

***trans*-4,5-Dihydroxy-1-methylamino-2-phenylindan (5) Hydrobromide**——To a mixture of **30**·HBr (prepared from its base (0.9 g)) and CH_2Cl_2 (12 ml) was added boron tribromide (1.5 ml) at −78° under N_2. The mixture was stirred at −78° for 45 min and at room temperature for additional 1 hr. The mixture was decomposed by addition of MeOH and evaporated. Recrystallization from isopropylalcohol–ether gave 0.9 g (86%) of the *trans* isomer (**5**), mp 146—148°. NMR (d_6-DMSO): 2.9—4.1 (3H, m), 4.5—4.7 (1H, m), 6.86 (1H, d, J=8, Ar-H), 7.06 (1H, d, J=8, Ar-H), 7.29 (5H, s, C_6H_5), 8.0—9.7 (4H, m). *Anal.* Calcd. for $C_{16}H_{17}NO_2$·HBr: C, 57.15; H, 5.40; N, 4.17; Br, 23.77. Found: C, 57.00; H, 5.53; N, 4.05; Br, 23.99.

***cis*-4,5-Dihydroxy-1-methylamino-2-phenylindan (6) Hydrobromide**——The *cis* isomer (**31**·HBr) (prepared from its free base (0.5 g)) was demethylated as described above to give 0.6 g (98%) of the *cis* isomer **6**·HBr. Leaflets from isopropylalcohol–ether, mp 139—142°. NMR (D_2O): 2.58 (3H, s, NCH_3), 3.0—4.1 (3H, m, $-CH_2CH-$), 4.65 (1H, d, J=6, -CH-N), 6.98 (1H, d, J=8, Ar-H), 7.15 (1H, d, J=8, Ar-H), 7.58 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{16}H_{17}NO_2$·HBr: C, 57.15; H, 5.40; N, 4.17; Br, 23.77. Found: C, 57.01; H, 5.48; N, 4.02; Br, 23.60.

β-(2,3-Dimethoxyphenyl)-α-phenylpropyl Methanesulfonate (32)——A solution of the carboxylic acid (**25**) (20 g) in EtOH was refluxed under pouring hydrogen chloride for 3 hr. The mixture was evaporated and taken in benzene. The solution was washed with 5% $NaHCO_3$ and evaporated to give 22 g of ethyl β-(2,3-dimethoxyphenyl)-α-phenylpropionate as a crude oil. A solution of this ester in dry ether (40 ml) was added to a stirred mixture of $LiAlH_4$ (5 g) and dry ether (300 ml) and the mixture was refluxed for 1 hr. Usual work-up gave 19 g of β-(2,3-dimethoxyphenyl)-α-phenylpropylalcohol as an oil. To a solution of this carbinol in pyridine (80 ml) was added mesyl chloride (8 ml) with stirring under ice-cooling for 20 min. The mixture was stirred at room temperature for 2 hr, poured onto ice-water, and extracted with benzene. The extracts were washed with 10% HCl and then H_2O. Evaporation of the solvent gave a pale yellow oil (**32**) (23 g), which was used to the next step.

γ-(2,3-Dimethoxyphenyl)-β-phenylbutyric Acid (33)——A mixture of **32** (23 g), NaCN (10 g) and DMSO (250 ml) was stirred at 90° for 1.5 hr. The mixture was poured onto ice-water and extracted with benzene.

Evaporation of the dried extracts gave 19 g of γ-(2,3-dimethoxyphenyl)-β-phenylbutyronitrile as a yellow oil. A mixture of this nitrile, KOH (12 g), H_2O (20 ml) and ethylene glycol (170 ml) was stirred at 135—140° for 25 hr. Usual work-up gave a brown oil **33** (19 g), which was used to the next step.

5,6-Dimethoxy-3-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (**34**)——A mixture of **33** (19 g) and PPA (300 g) was stirred at 95° for 1.5 hr. The mixture was poured onto ice-water and extracted with $CHCl_3$. The extracts were washed with 5% $NaHCO_3$ and then H_2O. Evaporation of the dried extracts gave, after recrystallization from AcOEt, 13 g (66% from **25**) of colorless needles (**34**), mp 129—131°. NMR: 2.6—3.7 (5H, m), 3.80, 3.93 (6H, each s, 2×OCH_3), 6.92 (1H, d, J=9, Ar–H), 7.36 (5H, s, C_6H_5), 7.92 (1H, d, J=9, Ar–H). *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.54.

5,6-Dimethoxy-1-methylamino-3-phenyl-1,2,3,4-tetrahydronaphthalene (**36**)——To a mixture of the ketone (**34**) (0.5 g), methylamine (0.55 g) and C_6H_6 (30 ml) was added a solution of $TiCl_4$ (0.10 g) in C_6H_6 (5 ml). The mixture was worked up in the same manner as that described above to give a crude residue of the imine (**35**). To a mixture of this imine and MeOH (30 ml) was added $NaBH_4$ (200 mg) and stirring was continued at room temperature for 3 hr. The mixture was decomposed by H_2O, concentrated, and extracted with ether. Evaporation of the dried extracts gave, after recrystallization from AcOEt–isopropylether, 400 mg (76%) of colorless needles (**36**), mp 118—119.5°. NMR: 1.40 (1H, s, NH, disappeared on addition of D_2O), 2.47 (3H, s, N–CH_3), 2.3—3.5 (4H, m), 3.77, 3.85 (6H, each s, 2×OCH_3), 3.9—4.2 (1H, m, N–CH–CH_2–), 6.82 (1H, d, J=9, Ar–H), 7.32 (5H, s, C_6H_5), 7.36 (1H, d, J=9, Ar–H). *Anal.* Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.98; H, 7.85; N, 4.70.

5,6-Dihydroxy-1-methylamino-3-phenyl-1,2,3,4-tetrahydronaphthalene (**7**) **Hydrobromide**——To a mixture of **36**·HBr [prepared from its free base (1 g)] and CH_2Cl_2 (20 ml) was added boron tribromide (4.2 g) with stirring at −78°. The mixture was worked up in the same manner as that described above to give 0.92 g (78%) of **7**·HBr. Colorless granules from EtOH–ether, mp 134—138°. *Anal.* Calcd. for $C_{17}H_{19}NO_2$·HBr·1/4H_2O: C, 57.55; H, 5.82; N, 3.95; Br, 22.53. Found: C, 57.33; H, 5.80; N, 3.91; Br, 22.37.

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