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The Syntheses and β-Adrenoceptor Activities of N-Substituted 2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols

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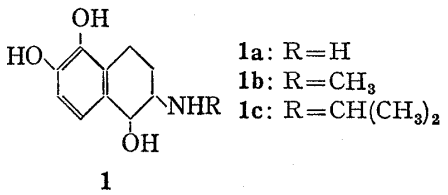
A series of N-substituted 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**), which are comformationally rigid derivatives of adrenergic catecholamine, were synthesized *via* three routes; namely, the synthetic route in which the final step is 1) the reduction of 1-carbonyl group, 2) N-substitution by reductive alkylation of 2-amino group, or 3) removal of protecting groups of the catechol moiety. Several pairs of 1,2-*cis* and *trans* isomers of **1** were prepared by stereoselective reactions or by separation of each stereoisomer with column chromatography or fractional crystallization. Thus, *trans*-amino alcohol (**9**-*trans*) was afforded by reduction of 2-amino-5,6-dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (**13**) with sodium borohydride, while the *cis* isomer (**9**-*cis*) was obtained from 7,8-dibenzyloxy-1,2-dihydronaphthalene (**19**) *via* an aziridine intermediate. Several of **1** exhibited excellent β_2-adrenoceptor activity superior to *l*-isoproterenol, the *trans* derivative being more potent than the *cis* isomer.

Keywords——β-adrenoceptor agonist; tetrahydronaphthalenol; β_2-sympathomimetic activity; rigid catecholamine; catecholamine analogues

In the preceding paper we reported the syntheses of 2-amino-,2-methylamino- and 2-isopropylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1a—c**), which are considered conformationally more rigid analogs of noradrenaline, adrenaline and isoproterenol, respectively.[2] Pharmacological studies of these analogs have revealed that all the three compounds exhibit potent β-adrenoceptor agonist activities with predominant β_2-directing properties.[3] It has been shown that modifications of the nitrogen substituent of adrenergic catecholamines often result in remarkable increases of the β-mimetic activities.[4] This fact prompted us to further modifications of the nitrogen substituent of **1**. The present paper describes the syntheses of a variety of N-substituted 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols as well as the adrenoceptor activities of the compounds.



1

1a: R=H
1b: R=CH_3
1c: R=$CH(CH_3)_2$

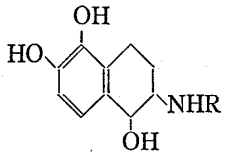
Chart 1

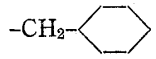
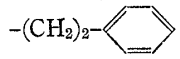
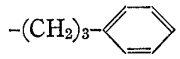
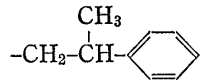
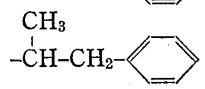
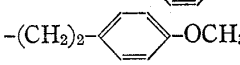
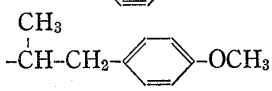
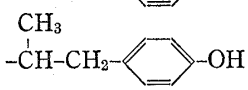
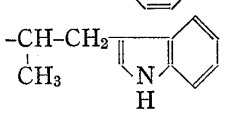
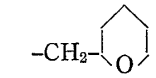
Chemistry

Methods employed for the syntheses of **1** are classified into three types based on the final step of the procedures, namely the synthetic method in which the final step is 1) the reduction of 1-carbonyl group into hydroxy group, 2) reductive alkylation of 2-amino group in **1a**, and 3) removal of protecting groups of the catechol moiety. The syntheses of the derivatives of **1** were carried out by any of these three methods taking into account chemical properties

1) Location: *Juso-Honmachi, Yodogawa-ku, Osaka, 532, Japan.*
2) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **25**, 632 (1977).
3) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
4) See for example, D.J. Triggle, "Medicinal Chemistry," 3rd ed., Vol. 2, ed. by A. Burgerd, Willy-Interscience, Inc., New York, N.Y., 1970, p. 1235.

TABLE I. N-Substituted 2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (1)[5]



No.	R	Salt	Yield[a]	mp (°C) (dec.)	Formula	Analysis (%) Calcd. (Found) C	H	N
1a-*trans*	H	HBr	68	210—213	$C_{10}H_{13}NO_3 \cdot HBr \cdot H_2O$	40.84 (40.94)	5.48 (5.49)	4.76 (4.43)
1a-*cis*	H	HBr	34	180—190[b]	$C_{10}H_{13}NO_3 \cdot HBr$	43.50 (43.04)	5.11 (5.20)	5.07 (4.95)
1c-*trans*	iso-C_3H_7	Fumarate	74	180—210[b]	$C_{13}H_{19}NO_3 \cdot 1/2C_4H_4O_4 \cdot C_2H_5OH$	59.81 (60.00)	7.97 (8.00)	4.10 (4.25)
1c-*cis*	iso-C_3H_7	Fumarate	87	179—181	$C_{13}H_{19}NO_3 \cdot 1/2C_4H_4O_4 \cdot H_2O$	57.50 (57.56)	7.40 (7.25)	4.47 (4.31)
1d-*trans*	C_2H_5	HBr	61,[c] 76[d]	169—170	$C_{12}H_{17}NO_3 \cdot HBr \cdot H_2O$	47.38 (47.52)	5.96 (6.12)	4.60 (4.50)
1d-*cis*	C_2H_5	Fumarate	49	160—162	$C_{12}H_{17}NO_3 \cdot 1/2C_4H_4O_4 \cdot H_2O$	56.17 (55.72)	7.07 (7.00)	4.68 (4.68)
1e	*n*-C_3H_7	HBr	48	167—168	$C_{13}H_{19}NO_3 \cdot HBr \cdot H_2O$	46.43 (45.93)	6.59 (6.11)	4.17 (3.99)
1f	iso-C_4H_9	HBr	66	157—158	$C_{14}H_{21}NO_3 \cdot HBr \cdot H_2O$	48.01 (48.34)	6.91 (6.85)	4.00 (4.43)
1g-*trans*		Fumarate	64	211—214	$C_{14}H_{19}NO_3 \cdot 1/2C_4H_4O_4$	62.52 (62.03)	6.88 (7.04)	4.56 (4.32)
1g-*cis*		Fumarate	54	171—172	$C_{14}H_{19}NO_3 \cdot 1/2C_4H_4O_4 \cdot CH_3OH \cdot 2H_2O$	54.39 (54.50)	7.79 (7.50)	3.73 (3.28)
1h		HBr	35	228—239	$C_{15}H_{21}NO_3 \cdot HBr \cdot 1/2H_2O$	51.00 (50.55)	6.56 (6.26)	3.97 (3.80)
1i		HBr	41	230—236	$C_{16}H_{23}NO_3 \cdot HBr \cdot H_2O$	51.07 (51.26)	6.96 (6.55)	3.72 (3.56)
1j		HBr	25	161—164	$C_{17}H_{25}NO_3 \cdot HBr \cdot H_2O$	52.31 (52.74)	7.23 (7.07)	3.59 (3.32)
1k		HBr	25	146—149	$C_{18}H_{21}NO_3 \cdot HBr \cdot H_2O$	54.26 (54.64)	6.07 (6.04)	3.52 (3.16)
1l		HBr	44	136—139	$C_{19}H_{23}NO_3 \cdot HBr \cdot 1/2H_2O$	56.58 (56.60)	6.25 (5.89)	3.47 (3.25)
1m		HBr	24	149—151	$C_{19}H_{23}NO_3 \cdot HBr \cdot H_2O$	55.33 (55.77)	6.35 (5.88)	3.40 (3.51)
1n-*trans*		Fumarate	24	145—148	$C_{19}H_{23}NO_3 \cdot C_4H_4O_4$	64.32 (63.94)	6.34 (6.69)	3.26 (3.51)
1o		HBr	26	138—140	$C_{19}H_{23}NO_4 \cdot HBr \cdot H_2O$	53.28 (53.60)	6.12 (5.75)	3.27 (3.24)
1p-*trans*		Fumarate	21	150—153	$C_{20}H_{25}NO_4 \cdot C_4H_4O_4$	62.73 (63.17)	6.36 (6.59)	3.05 (3.10)
1q		Fumarate	45	137—141	$C_{19}H_{23}NO_4 \cdot C_4H_4O_4 \cdot H_2O$	59.60 (60.07)	6.31 (6.53)	3.02 (3.39)
1r-*trans*		Fumarate	38	*e*)	$C_{21}H_{24}N_2O_3 \cdot C_4H_4O_4$	64.09 (63.98)	6.02 (6.46)	5.98 (5.91)
1s	$-CH_2CH_2OCH_3$	HBr	47	156—159	$C_{13}H_{19}NO_4 \cdot HBr$	46.72 (46.46)	6.03 (5.99)	4.19 (4.29)
1t		HBr	15	155—158	$C_{16}H_{23}NO_4 \cdot HBr \cdot H_2O$	48.98 (49.20)	6.68 (6.49)	3.57 (3.54)

a) Yield of the final process, see Experimental. *b*) Decomposed gradually. *c*) Prepared by Method 1.
d) Prepared by Method 3. *e*) Showed indefinite mp.

of the intermediates and the products. The derivatives prepared in this paper are listed in Table I.[5]

Reductive alkylation of 2-amino-5,6-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (**2**)[2] by the reaction with a ketone in the presence of lithium cyanoborohydride[6] gave N-substituted 2-aminotetralone (**3**). Compound **3** was hydrolyzed with hydrobromic acid into 5,6-dihydroxy derivatives (**4**), which was led to **1** by catalytic reduction. Compound **4** was also obtained by reductive alkylation of 2-amino-5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**5**),[2] prepared by the hydrolysis of **2**, with an aldehyde using palladium-charcoal as the catalyst. Derivatives **1h** and **1i** were prepared by the former route, **2**→**3**→**4**→**1**, and derivatives **1d**-*trans*, **1e** and **1f** were obtained by the latter route, **2**→**5**→**4**→**1**. The catalytic reduction of **4** leading to **1** generally required prolonged reaction time when palladium-charcoal was employed as the catalyst, while the use of platinium dioxide was often accompanied by the side reaction such that a phenyl group involved in the N-substituent was hydrogenated into a cyclohexyl group.

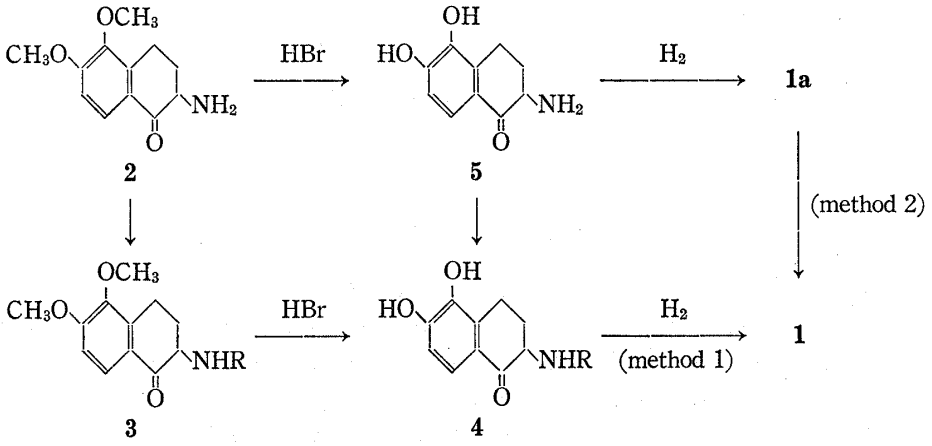


Chart 2

In an effort to overcome these disadvantages the second synthetic method, reductive alkylation of **1a**, was applied to the preparation of derivatives **1j**, **1k**, **1l**, **1m**, **1n**-*trans*, **1o**, **1p**-*trans*, **1q**, **1s**, and **1t**. Thus, **1a** was subjected to catalytic reduction over palladium-charcoal in the presence of the corresponding aldehyde or ketone under atmospheric pressure to afford **1**. In the preparation of **1t** the corresponding unsaturated aldehyde, acrolein dimer, was used as the reactant and the hydrogenation of the double bond was carried out simultaneously with the reductive alkylation.

It has been reported that 2-[2-(3-indolyl)-1-methyl]ethylamino-1-(3,4-dihydroxyphenyl)-ethanol possess potent β_2-adrenoceptor stimulanting action.[7] The unique substituent at the amino group of this compound prompted us to prepare the corresponding conformationally rigid derivative (**1r**). Since the indole moiety in the substituent was suspected to be rather unstable under the above-mentioned conditions of catalytic reduction, the preparation was carried out by using the third synthetic method, *i.e.* by reducing the 1-carbonyl group with a reducing reagent prior to removal of the protecting groups of the catechol moiety. Thus, 5,6-dibenzyloxy-2-hydroximino-3,4-dihydro-1(2*H*)-naphthalenone (**8**), prepared from 5,6-dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (**6**)[2] by formylation with ethyl formate to give 2-

5) In this paper configurations of the substituents at C_1–C_2 in the tetrahydronaphthalene derivatives are represented by affixing "*cis*" or "*trans*" behind the compound number. A compound number without the affix denotes that the compound consists of a mixture of 1,2-*cis* and *trans* isomers.

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

7) C.G. Van Arman, L.M. Miller, and M.P. O'Mailey, *J. Pharmacol. Exptl. Therap.*, **13**, 90 (1961).

hydroxymetylidene derivative (**7**) followed by treatment with sodium nitrite-acetic acid, was reduced with lithium aluminum hydride to afford 2-amino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (**9**). The reaction of **9** with 3-acetonylindole in the presence of lithium cyanoborohydride gave N-[2-(3-indolyl)-1-methyl]ethyl derivative (**10**: R=CH(CH$_3$)–CH$_2$–indol-3-yl), catalytic reduction of which over palladium-charcoal under a mild condition followed by treatment with fumaric acid yielded **1r**-*trans* as a fumarate.

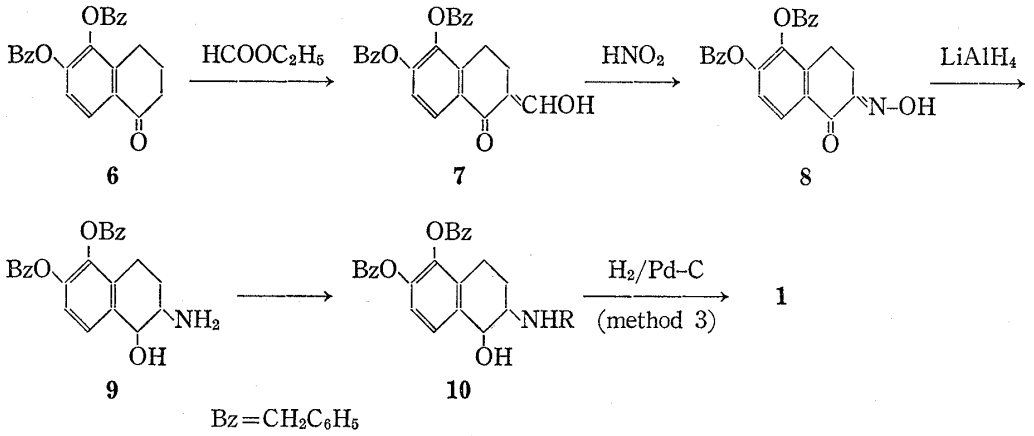


Chart 3

Since structure **1** involves two asymmetric centers, theoretically four stereoisomers exist with respect to the substituents at the 1- and 2-positions. In the above syntheses all the reactions producing 2-amino-1-alcohol moiety proceeded without stereoselectivity, giving mixtures of *cis* and *trans* isomers. Compounds **1**, therefore, were generally mixtures of *cis* and *trans* isomers except the cases of **1d**, **1n**, **1p**, and **1r**, where only *trans* isomers were preferentially crystallized from the solution of the mixture.[8] Our previous experiments have shown that in the case of the N-methyl derivative (**1**: R=CH$_3$) the *trans* isomer exhibits the β-adrenoceptor activity ten times as potent as that of the *cis* isomer.[3] The result seems to be of interest in connection with the actual spatial arrangement of an adrenergic catecholamine molecule at the receptor site. In order to further confirm the relationship between the activity and the configuration, preparations of several pairs of *cis* and *trans* isomers were undertaken with representative derivatives.

Two methods were considered for the preparation of those stereoisomers: One is the separation of one isomer from the other by utilizing fractional crystallization or chromatography at a certain stage of the synthesis, and the other is the synthesis by use of a stereoselective reaction. In the above cases of **1d**-*trans*, **1n**-*trans*, **1p**-*trans*, and **1r**-*trans*, *trans* isomers were separated on crystallization of the product at the final step. The preparation of isomers of N-isopropyl derivative (**1c**-*trans* and **1c**-*cis*) were carried out by separating each other at the stage of intermediate **10** (R=iso-C$_3$H$_7$). Thus compound **10** (R=iso-C$_3$H$_7$), obtained by the reaction of **9** with acetone and lithium cyanoborohydride, was led to an acetic acid salt. On recrystallization of the salt from ethanol–ethyl ether, only *cis* isomer was obtained as crystals. Neutralization of the filtrate followed by recrystallization of the resulting free base afforded **10**-*trans* (R=iso-C$_3$H$_7$). O-Benzyl groups of each isomer were removed by catalytic hydrogenation to afford **1c**-*cis* and **1c**-*trans*.

8) Although another set of diastereoisomers will exist in compounds **1m**, **1n**, **1p**, **1q**, **1r** and **1t**, in which the substituent R involves an asymmetric center, we have no evidence at present as to whether the isolated compounds correspond to one diastereoisomer or mixtures of the two isomers with respect to the asymmetric carbon in R.

The syntheses of isomers of **1a**, **1d** and **1g** were carried out by the use of stereoselective reactions. 5,6-Dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone oxime O-*p*-toluenesulfonate (**12**), which was obtained by the reaction of **6** with hydroxylamine affording an oxime (**11**) followed by treatment with *p*-toluenesulfonyl chloride in pyridine, was subjected to Neber rearrangement by treatment with potassium ethoxide in benzene to give 2-amino-5,6-dibenzyloxy-3,4-dihydro-1(2H)-naphthalenone (**13**). Reduction of **13** with sodium borohydride proceeded stereoselectively to give **9-*trans***, which was led to **1a-*trans*** by catalytic hydrogenation. The reaction of **9-*trans*** with cyclobutanone in the presence of lithium cyanoborohydride afforded **10-*trans*** (R=cyclobutyl), catalytic hydrogenation of which yielded **1g-*trans***. The compound **1a-*trans*** was also obtained by the following alternative route: Compound **9**, a *cis* and *trans* mixture, was treated with carbobenzyloxychloride to give N-carbobenzyloxy derivative (**14**). Oxidation of **14** with Jones reagent gave the corresponding ketone (**15**) which was identical with the sample obtained by carbobenzyloxylation of **13**. Reduction of **15** with sodium borohydride afforded **14-*trans***, from which **1a-*trans*** was derived by catalytic hydrogenation. Since reductive ethylation of **9-*trans*** by the reaction with acetaldehyde and lithium cyanoborohydride was found to be accompanied by side reactions, the stereoselective synthesis of **1d-*trans*** was achieved *via* the following route: 2-Acetylamino-5,6-dibenzyloxy-3,4-dihydro-1(2H)-naphthalenone (**16**) obtained by acetylation of **13** was reduced with sodium borohydride to give *trans*-acetamido alcohol (**17-*trans***). Reduction of **17-*trans*** with lithium aluminum hydride afforded **10-*trans*** ($R=C_2H_5$), which was led to **1d-*trans*** by catalytic reduction.

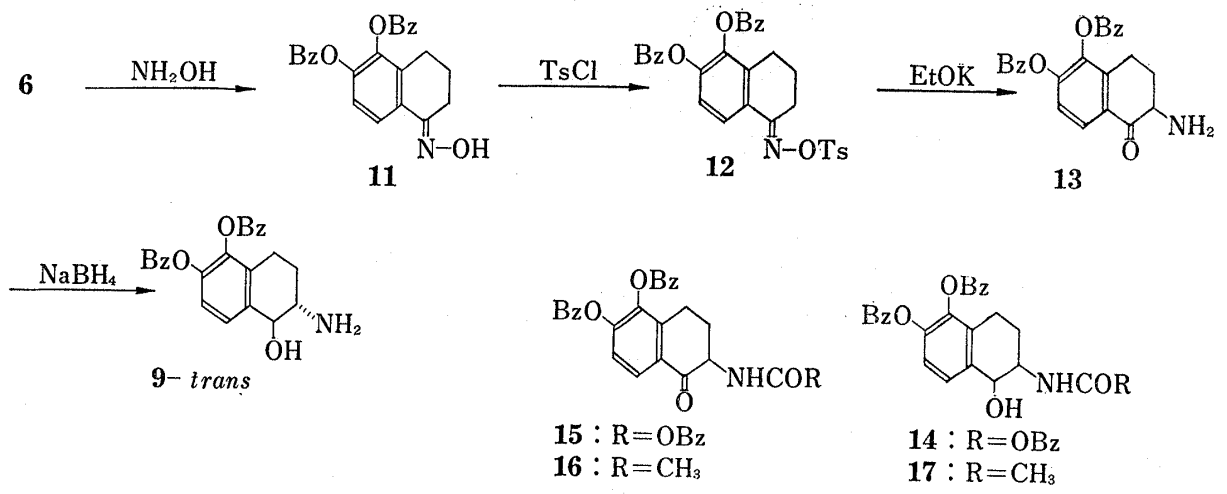


Chart 4

On the other hand, the corresponding *cis* isomers, **1a-*cis***, **1d-*cis*** and **1g-*cis***, were prepared by the following sequence of reactions. Reduction of **6** to the naphthalenol derivative (**18**) followed by dehydration with potassium bisulfate afforded 7,8-dibenzyloxy-1,2-dihydronaphthalene (**19**). Compound **19** was allowed to react with N-bromosuccinimide-sodium azide and the product was treated with lithium aluminum hydride to give conceivably 1,2-aziridino derivative,[9] which, without being isolated, was hydrolyzed with sulfuric acid to afford **9-*cis*** in 21% yield.[10] Debenzylation of **9-*cis*** by catalytic reduction furnished **1a-*cis***, while the

9) D. Van Ende and A. Krief, *Angew. Chem.*, **86**, 311 (1974).

10) The formation of *cis*-2-amino-1-hydroxyl derivative (**9-*cis***) from *cis*-1,2-azirino derivative is explained by the intervention of *trans*-2-amino-1-hydroxysulfonyloxy derivative, details of which are to be discussed in a forthcoming paper; H. Sugihara, K. Ukawa, A. Miyake, and Y. Sanno, *Chem. Pharm. Bull.* (Tokyo), "in press."

reaction of **9**-*cis* with cyclobutanone and lithium cyanoborohydride affording **10**-*cis* (R= cyclobutyl) followed by catalytic reduction gave rise to **1g**-*cis*. The synthesis of **1d**-*cis* was achieved *via* the same route as described for **1d**-*trans*. Thus, a *cis* and *trans* mixture of **9** was acetylated to give N,O-diacetate (**20**), from which **20**-*cis* was separated by column chromatography. Reduction of **20**-*cis* with lithium aluminum hydride gave **10**-*cis* ($R=C_2H_5$), which was led to **1d**-*cis* by catalytic reduction. Although **10**-*cis* ($R=C_2H_5$) would also be derived from **9**-*cis* by acetylation and the subsequent reduction, the method *via* **20**-*cis* appeared to be advantageous in view of the low yield in the conversion of **19** into **9**-*cis*.

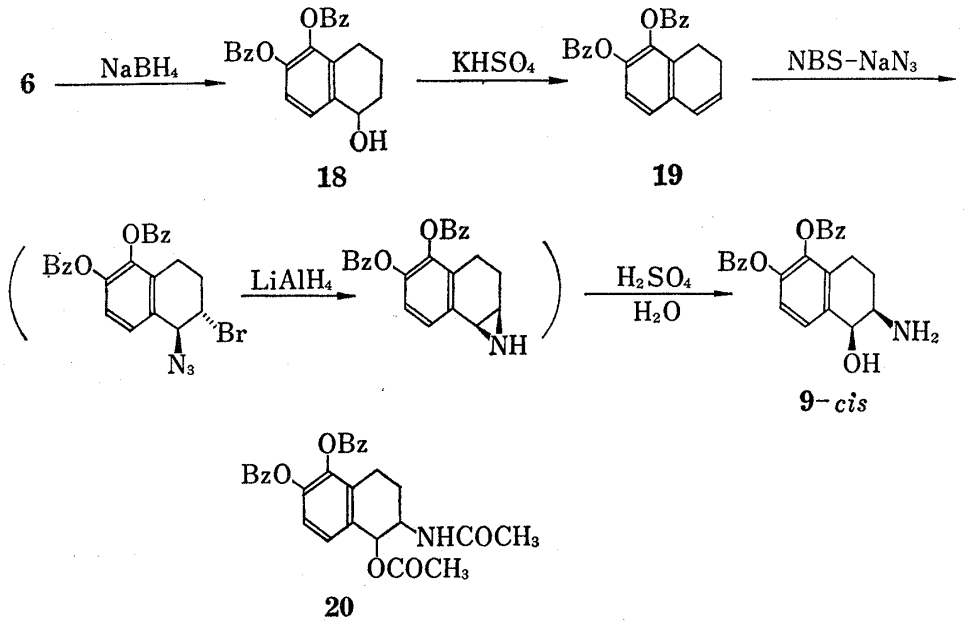
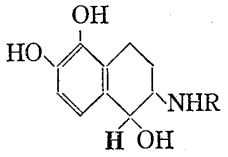
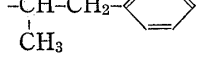
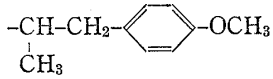
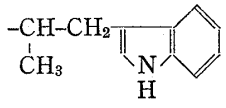


Chart 5

TABLE II. Chemical Shifts and Coupling Constants of C_1-H in the *cis* and *trans* Isomers of 2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol Derivatives (**1**) (in DMSO-d_6+D_2O, at 100 MHz)



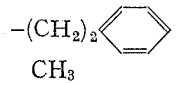
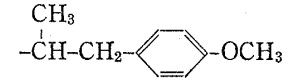
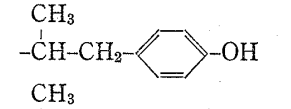
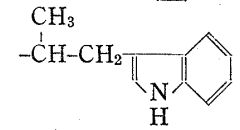
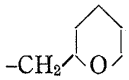
Compound No.	R	*trans* (ppm)	*trans* *J* (Hz)	*cis* (ppm)	*cis* *J* (Hz)
1a	H	4.53	9	4.59	1—2
1c	iso-C_3H_7	4.57	10	4.66	3
1d	C_2H_5	4.63	9	4.69	2
1g		4.56	9	4.66	3
1n		4.54	9	—	—
1p		4.60	9	—	—
1r		4.74	8	—	—

The *cis* and *trans* isomers of **1** derivatives can be readily distinguished from each other by the nuclear magnetic resonance (NMR) spectra of the proton at the 1-position.[2] In the *trans* series the signal was observed as a doublet with the coupling constant of 8—10 Hz, while the *cis* series showed a distinctly smaller coupling of constant 1—3 Hz. The results are summarized in Table II.

Biological Results

The β_1- and β_2-adrenoceptor activities of most of the derivatives **1** were measured *in vitro* using, respectively, isolated arterial preparations and tracheal strips of guinea pig according to the methods described in the previous paper.[3] It was observed that the β_2-sympathomimetic activity of several compounds, *e.g.* **1c**-*trans*, **1g**-*trans*, **1h**, **1o**, **1q**, and **1r**-*trans*, exceeded that of *l*-isoproterenol, despite the fact that they were mixture of two or four stereoisomers. In particular, **1g**-*trans* was about twenty-four times more potent than *l*-isoproterenol. In every set of 1,2-*cis* and *trans* isomers, the *trans* compound were significantly more potent than the *cis* counterpart consistently with the result for the previously

Table III. β-Adrenoceptor Activities of *d,l*-N-Substituted 2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**)

Compound No.	R	β_1-Activity[a]		*i.a.*[e]	β_2-Activity[b]		β_1/β_2
		n[c]	pD_2[d]		n[c]	pD_2[d]	
1a-*trans*	H	3	6.26±0.07	0.95	3	7.44±0.11	15.2
1a-*cis*	H	3	5.64±0.07	0.87	4	6.60±0.08	9.1
1c-*trans*	iso-C_3H_7	4	7.99±0.07	1.0	2	8.78[f]	6.2
1c-*cis*	iso-C_3H_7	3	6.07±0.08	1.0	2	6.76[f]	4.9
1d-*trans*	C_2H_5	4	7.51±0.27	1.0	3	7.71±0.26	1.6
1d-*cis*	C_2H_5	3	6.05±0.12	0.86	4	6.89±0.08	6.9
1e	*n*-C_3H_7	4	7.02±0.08	1.0	4	7.63±0.06	4.1
1f	iso-C_4H_9	4	6.42±0.24	0.8	4	7.42±0.07	10.0
1g-*trans*		8	8.67±0.07	1.0	7	9.27±0.17	4.0
1g-*cis*		3	6.57±0.10	0.92	3	7.15±0.10	3.8
1h		4	7.90±0.08	1.0	2	8.05[f]	1.4
1i		5	6.27±0.25	0.4	2	6.70[f]	2.7
1k		4	7.17±0.24	1.0	3	7.32±0.06	1.4
1o		5	8.34±0.19	1.0	5	8.71±0.03	2.4
1q		4	8.47±0.12	1.0	3	8.75±0.04	1.9
1r-*trans*		3	8.54±0.29	1.0	2	8.34[f]	0.6
1t		4	6.01±0.03	1.0	3	6.13±0.09	1.3
l-Isoproterenol		134	8.39±0.00	1.0	80	7.96±0.03	0.37

a) Positive chronotropic action in isolated guinea-pig atria.
b) Isolated guinea-pig tracheal chain.
c) Number of experiments.
d) Values are expressed as Mean ±S.E.
e) Intrinsic activity. All the compounds showed *i.a.*=1.0 for the trachea.
f) Mean.

reported N-methyl derivative.[3] The results are summarized in Table III. The separation of the β_1- and β_2-activity for each compound was expressed in terms of separation ratio β_1/β_2, a value obtained by dividing ED_{50} for the arterial test by ED_{50} for tracheal test. As can be seen from Table III, all the compounds tested showed β_2-selectivity superior to isoproterenol.

Experimental

All melting points were measured on a micro hot-stage apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 215 spectrophotometer. NMR spectra were recorded on Varian T-60 or HA-100 using Me_4Si as a standard.

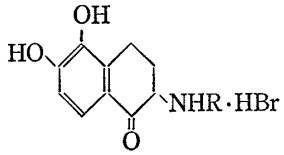
2-Cyclopentylamino-5,6-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (3: R=cyclopentyl)——To a stirred solution of 2-amino-5,6-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride (2)[2] (1.0 g) and cyclopentanone (30 g) in MeOH (30 ml) was added portionwise $LiBH_3CN \cdot 2$ dioxane[6] (1.4 g) under a stream of nitrogen at 0—5°. The mixture was stirred at room temperature for 3 hr and evaporated *in vacuo* after addition of 3 N HCl (10 ml). The residue was extracted with water and benzene. The aqueous phase was decolorized with activated charcoal and evaporated to dryness. Recrystallization of the residue from EtOH gave 660 mg (53%) of 3·HCl (R=cyclopentyl) as colorless granules, which showed no definite mp, decomposing gradually between 160° and 180°. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). *Anal.* Calcd. for $C_{17}H_{23}NO_3 \cdot HCl$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.48; H, 7.50; N, 4.12.

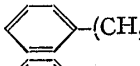
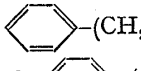
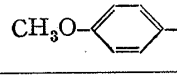
2-Cyclohexyl-5,6-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (3: R=cyclohexyl)——Compound **2** (1.0 g) was allowed to react with cyclohexanone (30 ml) as described above and the resulting crude product was recrystallized from EtOH–ether to give 750 mg (57%) of 3·HCl (R=cyclohexyl) as colorless powder, which showed no definite mp, decomposing gradually between 165° and 220°. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). *Anal.* Calcd. for $C_{18}H_{25}NO_3 \cdot HCl$: C, 63.61; H, 7.71; N, 4.12. Found: C, 63.42; H, 7.81; N, 4.33.

2-Substituted Amino-5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone Hydrobromide (4) (Table IV)——General Procedure: a) A mixture of 3·HBr (1 g), 47% HBr (10 ml) and Ac_2O (3 ml) was refluxed for 2—3 hr. After the mixture was evaporated to dryness under reduced pressure, the crystalline residue was triturated with EtOH or EtOAc and filtered to give 4·HBr.

b) To a solution of 2-amino-5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone hydrobromide (5)[2] in 10—50 volumes of EtOH was added 10—50 equimolar amount of an aldehyde, and the mixture was catalytically hydrogenated over 5% pd-C (0.5—2 epuivalent weight) under atmospheric pressure at room tempera-

Table IV. N-Substituted 2-Amino-5,6-dihydroxy-3,4-dihydro-1(2H)-naphthalenone (4)



R	Method[a]	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd. (Found) C	H	N
C_2H_5	B	36	210—215	$C_{12}H_{15}NO_3 \cdot HBr$	47.70 (47.54)	5.34 (5.28)	4.64 (4.67)
n-C_3H_7	B	58	215—220	$C_{13}H_{17}NO_3 \cdot HBr$	49.38 (49.66)	5.74 (5.61)	4.43 (4.27)
iso-C_4H_9	B	83	205—209	$C_{14}H_{19}NO_3 \cdot HBr$	50.92 (50.90)	6.11 (6.06)	4.24 (4.31)
	A	70	220—223	$C_{15}H_{19}NO_3 \cdot HBr$	52.64 (52.59)	5.89 (5.87)	4.09 (4.06)
	A	57	233—237	$C_{16}H_{21}NO_3 \cdot HBr$	53.94 (53.64)	6.22 (6.20)	3.93 (3.77)
	B	49	210—218	$C_{18}H_{19}NO_3 \cdot HBr$	57.15 (57.26)	5.33 (5.12)	3.70 (3.80)
	B	51	215—217	$C_{19}H_{21}NO_3 \cdot HBr$	58.17 (58.39)	5.65 (5.69)	3.57 (3.18)
	B	54	198—203	$C_{19}H_{21}NO_4 \cdot HBr$	55.89 (56.30)	5.43 (5.38)	3.43 (3.05)

a) A: HBr hydrolysis of **3**. B: Reductive alkylation of **5** with an aldehyde.

ture until the absorption of hydrogen ceased. After the catalyst was removed by filtration, the filtrate was concentrated *in vacuo* and resulting crystals were collected by filtration to give **4**·HBr. In cases no crystals were deposited during the concentration, the solution was evaporated to dryness and EtOH–ether or ether was added to the residue to deposit **4** as crystals.

5,6-Dibenzyloxy-2-hydroxymethylene-3,4-dihydro-1(2*H*)-naphthalenone (7)——To an ice-cooled mixture of dry benzene (30 ml), ethyl formate (2.5 g), and MeONa powder prepared from Na (0.77 g) and MeOH (12 ml), was added dropwise a solution of 5,6-dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (**6**)[2] (6 g) in dry benzene (35 ml) under nitrogen. After being stirred at room temperature for 4 hr, the mixture was shaken with a mixture of ice water (200 ml) and $CHCl_3$ (200 ml). The organic layer was separated, washed with 3 N HCl (200 ml) and then water (200 ml), dried over Na_2SO_4 and evaporated to afford 6 g of residue, which was submitted to column chromatography on silica gel using benzene as an eluant. From the first fraction was obtained 655 mg (10%) of 5,6-dibenzyloxy-2-hydroxymethylene-1(2*H*)-naphthalenone, mp 115—116° (recrystallized from cyclohexane). *Anal.* Calcd. for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 77.94; H, 5.18. Evaporation of the second fraction followed by recrystallization of the residue from cyclohexane afforded 4.33 g (67%) of **7** as pale yellow prisms, mp 105—108°. *Anal.* Calcd. for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.85; H, 5.49.

5,6-Dibenzyloxy-2-hydroxyimino-3,4-dihydro-1(2*H*)-naphthalenone (8)——To a solution of **7** (3.27 g) in a mixture of CH_2Cl_2 (36 ml), water (9 ml) and AcOH (180 ml) was added dropwise a solution of 1.18 g of $NaNO_2$ in water (15 ml) at 0°. After being stirred at 0° for 30 min, the mixture was extracted with 200 ml of CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated. Filtration of the resulting crystals and recrystallization from tetrahydrofuran (THF) gave 2.25 g (69%) of **8** as colorless needles, mp 203—208°. *Anal.* Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.64; H, 5.32; N, 3.30.

5,6-Dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime (11)——A mixture of **6** (10 g) and NH_2OH·HCl (10 g) in pyridine (50 ml) was heated at 120° for 1 hr. After cooling, the mixture was poured into water. The resulting crystals were collected by filtration and recrystallized from ethanol to give 9.4 g (90%) of **11** as colorless needles, mp 135—137°. *Anal.* Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.46; H, 6.28; N, 3.85.

5,6-Dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-*p*-Toluenesulfonate (12)——To an ice-cooled solution of **11** (10.4 g) in pyridine (40 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (11 g) in pyridine (40 ml) with stirring. After being stirred for 30 min under ice-cooling and further for 1 hr at room temperature, the mixture was poured into water and the resulting crystals were collected by filtration. Recrystallization from MeOH gave 13.2 g (90%) of **12**, mp 143.5—145°. *Anal.* Calcd. for $C_{31}H_{29}NO_5S$: C, 70.60; H, 5.35; N, 2.42. Found: C, 70.57; H, 5.54; N, 2.66.

2-Amino-5,6-dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (13)——To a solution of **12** (13.2 g) in dry benzene (150 ml) was added dropwise a solution of EtOK, prepared from K (1.1 g) and abs. EtOH (30 ml), under ice-cooling. After being stirred under cooling for further 5 hr, the mixture was allowed to stand in a refrigerator for 5 days. The insoluble substance was removed by filtration and to the filtrate was added 10% HCl (100 ml), whereupon crystals deposited in the benzene layer. After the aqueous layer was removed, to the benzene layer was added ether (200 ml) and the crystals were collected by filtration. Treatment with activated charcoal followed by recrystallization from EtOH gave 3.6 g (35%) of **13**·HCl as colorless needles, which showed no definite mp, decomposing gradually below 210°. *Anal.* Calcd. for $C_{24}H_{23}NO_3$·HCl: C, 70.32; H, 5.90; N, 3.42. Found: C, 70.16; H, 5.76; N, 3.17.

5,6-Dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (18)——To a solution of **6** (12 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (3 g) and the mixture was stirred at room temperature for 15 min. To the mixture was added an excess of water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated under reduced pressure. Recrystallization of the residue from petroleum ether afforded 10 g (83%) of **18**, mp 84—86°. *Anal.* Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.60; H, 6.70.

7,8-Dibenzyloxy-1,2-dihydronaphthalene (19)——To a solution of **18** (10 g) in benzene (150 ml) was added $KHSO_4$ (5 g) and the mixture was refluxed in a flask equipped with a water separator. After 1 hr, the reaction mixture was washed with water, dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from MeOH gave 8.5 g (90%) of **19** as colorless needles, mp 67—69°. *Anal.* Calcd. for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 83.81; H, 6.46.

2-Amino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (9)——To a solution of **12** (11.8 g) in dry THF (330 ml) was added $LiAlH_4$ (6.0 g) and the mixture was refluxed for 5 hr. To the cooled mixture was added portionwise 20 ml of water with stirring and the supernatant was separated by decantation. The residue was rinsed with ether (300 ml) and the ethereal solution was combined with the supernatant. The combined solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was taken up in AcOEt (10 ml) and then a solution of *p*-toluenesulfonic acid (TsOH) (6 g) in ether (300 ml) was added to the solution. Recrystallization of the resulting precipitate from EtOH–ether gave 10.1 g (61%) of **9**·TsOH (a mixture of *cis* and *trans*) as colorless powder, which sintered at 166—189° and decomposed gradually between 220° and 250°. *Anal.* Calcd. for $C_{24}H_{25}NO_2 \cdot C_7H_8O_3S$: C, 67.99; H, 6.07; N, 2.56. Found: C, 68.01; H, 6.19; N, 2.47. NMR (DMSO-d_6+H_2O) δ: 4.78 (1H, m, C_1–H).

***trans*-2-Amino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (9-*trans*)**——To a solution of **13** (1.0 g) in MeOH (50 ml) was added portionwise $NaBH_4$ (1.2 g) with stirring at room temperature. After the addition was completed, stirring was continued for 20 min. The reaction mixture was diluted with 300 ml of water and extracted twice with 100 ml portions of $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting crystals were filtered after addition of ether (20 ml) to afford 0.75 g (82%) of 9-*trans*, mp 140—143°. *Anal.* Calcd. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.67; H, 6.59; N, 3.59. NMR ($CDCl_3$) δ: 4.26 (1H, d, C_1–H, J=8 Hz).

***cis*-2-Amino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (9-*cis*)**——To a solution of **19** (3.8 g) in dimethoxyethane (DME) (80 ml) was added a solution of NaN_3 (10 g) in water (20 ml). To the mixture was added N-bromosuccinimide (4.9 g) in portions within a period of 10 min while the mixture was vigorously stirred under cooling with ice-NaCl. After the stirring was continued for further 10 min, the mixture was poured into water and extracted with ether (200 ml). The extract, dried over Na_2SO_4, was added dropwise to a suspension of $LiAlH_4$ (20 g) in ether (300 ml) and the mixture was refluxed with stirring for 2.5 hr. After cooling, the mixture was decomposed by addition of water. The ether layer was separated, dried over Na_2SO_4, and evaporated. The residue was dissolved in a mixture of dioxane (100 ml) and 5% H_2SO_4 (100 ml), and allowed to stand overnight. The mixture was poured into water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The residue was dissolved in a solution of excess oxalic acid in MeOH and diluted with ether to deposit crystals, which were collected by filtration and recrystallized from MeOH to give 1.0 g (21%) of 9-*cis* oxalate as colorless crystalline powder, mp 185—195° (dec.). *Anal.* Calcd. for $C_{24}H_{25}NO_3 \cdot 1/2C_2H_2O_4 \cdot 1/2H_2O$: C, 69.91; H, 6.34; N, 3.26. Found: C, 69.48; H, 5.96; N, 3.14.

The free base of 9-*cis* was obtained by neutralization of the oxalate followed by crystallization from $CHCl_3$–ether; colorless needles, mp 126—129° (dec.). *Anal.* Calcd. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.94; H, 6.67; N, 3.46.

The TsOH salt of 9-*cis* was prepared by addition of MeOH solution of TsOH to the free base of 9-*cis*; colorless crystalline powder, mp 157—160° (dec.). *Anal.* Calcd. for $C_{24}H_{25}NO_3 \cdot C_7H_8O_3S$: C, 67.99; H, 6.07; N, 2.56. Found: C, 68.01; H, 5.99; N, 2.54. NMR (DMSO-d_6+D_2O) δ: 4.62 (1H, d, C_1-H, J=3 Hz).

2-Acetylamino-5,6-dibenzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (16)——A solution of **13** (1.0 g) in Ac_2O (50 ml) was heated on a steam bath at 90° for 30 min. After excess Ac_2O was removed by evaporation, to the residue was added ether (20 ml) and petr. ether (50 ml), and the resulting crystals were collected by filtration to give 0.8 g (79%) of **16** as colorless needles, mp 181—184°. *Anal.* Calcd. for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 75.53; H, 6.08; N, 3.10.

***trans*-2-Acetylamino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (17-*trans*)**——To a solution of **16** (8.3 g) in a mixture of $CHCl_3$ (100 ml) and MeOH (200 ml) was added portionwise $NaBH_4$ (4 g) with stirring at room temperature. After 1 hr, to the mixture was added water (500 ml). The $CHCl_3$ layer was separated and the aqueous layer was extracted with $CHCl_3$ (200 ml). The combined $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. To the residue was added 50 ml of ether and the resulting crystals were collected by filtration to give 8.0 g (96%) of 17-*trans*, mp 200—203°. *Anal.* Calcd. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.36. Found: C, 74.81; H, 6.57; N, 3.08. NMR (DMSO-d_6+D_2O) δ: 4.47 (1H, d, C_1–H, J=7 Hz).

***cis*- and *trans*-2-Acetylamino-5,6-dibenzyloxy-1,2,3,4-tetrahydro-1-naphthyl Acetate (20-*cis* and 20-*trans*)**——To a solution of 9·TsOH (a mixture of *cis* and *trans*) (1.5 g) in pyridine (20 ml) was added Ac_2O (4 g) and the mixture was warmed at 50—60° for 1 hr. After cooling, the mixture was diluted with 100 ml of water. The resulting crystals were collected by filtration and submitted to column chromatography on silica gel eluted with $CHCl_3$–AcOEt (1: 1). From the first fraction was obtained 0.4 g (25%) of 20-*trans*, mp 168—171°. *Anal.* Calcd. for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.18; H, 6.26; N, 3.03. NMR ($CDCl_3$) δ: 5.82 (1H, d, C_1–H, J=7 Hz).

The second fraction afforded 1.0 g (62%) of 20-*cis*, mp 215—217°. *Anal.* Calcd. for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.15; H, 6.32; N, 3.00. NMR ($CDCl_3$) δ: (5.98 1H, d, C_1–H, J=3 Hz).

5,6-Dibenzyloxy-2-[2-(3-indolyl)-1-methyl]ethylamino-1,2,3,4-tetrahydro-1-naphthalenol [10: R=2-(3-indolyl)-1-methylethyl]——To a solution of 9·TsOH (1.2 g) in MeOH (30 ml) was added 3-indolylacetone (1.7 g) and $LiBH_3CN \cdot 2$ dioxane (2.0 g). After stirring the mixture for 6 hr at room temperature, the mixture was poured into water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was submitted to column chromatography on silica gel. After elution of impurity with acetone–benzene (1: 2), further elution with acetone–benzene (1: 1) afforded 0.7 g (61%) of **10** [R=2-(3-indolyl)-1-methylethyl] as amorphous powder. For the purpose of elemental analysis, a portion of the compound was led to the hydrogen fumarate, colorless crystalline powder, mp 114—118° (dec.). *Anal.* Calcd. for $C_{35}H_{36}N_2O_3 \cdot C_4H_4O_4$: C, 72.20; H, 6.22; N, 4.32. Found: C, 72.40; H, 6.04; N, 4.07.

***cis*- and *trans*-5,6-Dibenzyloxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (10-*cis*: R=iso-C_3H_7 and 10-*trans*: R=iso-C_3H_7)**——To a stirred suspension of 9·TsOH (a *cis* and *trans* mixture) (2.1 g) in a mixture of MeOH (30 ml) and acetone (35 ml) was added portionwise $LiBH_3CN \cdot 2$ dioxane (2 g) under nitrogen at 0—2°. After stirring overnight at room temperature, water was added to the mixture and the solvent was evaporated *in vacuo*. The residue was extracted with EtOAc and to the extract, having been washed with water and dried over Na_2SO_4, was added AcOH (0.3 g). After evaporation of the mixture, the residue was

recrystallized twice from EtOH–ether to give 0.87 g (43%) of **10**-*cis* (R=iso-C_3H_7)·AcOH, mp 111—112° (dec.). *Anal.* Calcd. for $C_{27}H_{31}NO_3 \cdot CH_3COOH \cdot C_2H_5OH$: C, 71.10; H, 7.89; N, 2.67. Found: C, 70.53; H, 7.73; N, 2.68. NMR ($CDCl_3$+NaOD) δ: 44.48 (1H, d, C_1–H, J=4.2 Hz).

The mother liquor of the first recrystallization was evaporated, neutralized with 1 N NaOH, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of the residue from *n*-hexane gave 0.46 g (29%) of **10**-*trans* (R=iso-C_3H_7) as colorless needles, mp 94—99°. *Anal.* Calcd. for $C_{27}H_{31}NO_3$: C, 77.66; H, 7.48; N, 3.35. Found: C, 77.59; H, 7.40; N, 3.28. NMR ($CDCl_3$) δ: 4.29 (1H, d, C_1–H, J=7.8 Hz).

***trans*-5,6-Dibenzyloxy-2-cyclobutylamino-1,2,3,4-tetrahydro-1-naphthalenol (10-*trans*: R=cyclobutyl)**——To a stirred solution of **9**-*trans* (0.84 g) and cyclobutanone (1 g) in MeOH (30 ml) was added portionwise $LiBH_3CN \cdot 2$ dioxane (2 g) and the mixture was stirred for 4.5 hr under ice-cooling. After addition of water (3 ml), the mixture was evaporated *in vacuo*. The residue was extracted with AcOEt, and to the extract, after being washed with water and dried over Na_2SO_4, was added a solution of fumaric acid (90 mg) in EtOH (2 ml). The resulting crystals were collected by filtration to give 0.48 g (65%) of **10**-*trans* (R=cyclobutyl) fumarate as colorless crystalline powder, mp 174—175° (dec.). *Anal.* Calcd. for $C_{28}H_{31}NO_3 \cdot 1/2C_4H_4O_4$: C, 73.90; H, 6.82; N, 2.87. Found: C, 73.49; H, 6.68; N, 2.91. NMR (DMSO-d_6) δ: 4.41 (1H, d, C_1-H, J=8.4 Hz).

***cis*-5,6-Dibenzyloxy-2-cyclobutylamino-1,2,3,4-tetrahydro-1-naphthalenol (10-*cis*: R=cyclobutyl)**——To a stirred solution of 9-*cis*·TsOH (1 g), cyclobutanone (1 g) in MeOH (30 ml) was added portionwise $LiBH_3CN$·2 dioxane (1.5 g). After being stirred for 24 hr at room temperature, the mixture was acidified with 10% HCl, poured into water, neutralized with $NaHCO_3$, and then extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was dissolved in a solution of fumaric acid (150 mg) in EtOH (3 ml). To the solution was added dropwise ether to precipitate 0.58 g (62%) of **10**-*cis* (R=cyclobutyl) fumarate as colorless crystalline powder, mp 86—88°. *Anal.* Calcd. for $C_{28}H_{31}NO_3 \cdot 1/2C_4H_4O_4 \cdot 1/2C_2H_5OH$: C, 72.92; H, 7.11; N, 2.74. Found: C, 72.84; H, 7.14; N, 2.80. NMR (DMSO-d_6) δ: 4.62 (1H, d, C_1–H, J=2 Hz).

***trans*-5,6-Dibenzyloxy-2-ethylamino-1,2,3,4-tetrahydro-1-naphthalenol (10-*trans*: R=C_2H_5)**——To a stirred suspension of $LiAlH_4$ (7 g) in THF (150 ml) was added a solution of **17**-*trans* (8 g) in THF (200 ml), and the mixture was refluxed for 2 hr. After cooling, to the mixture was added 300 ml of ether, and excess reagent and aluminum complex were decomposed by a dropwise addition of water under ice-cooling. The mixture was filtered and washed with $CHCl_3$ (300 ml). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in ether (100 ml) and allowed to stand overnight, whereupon 5.4 g (70%) of **10**-*trans* (R=C_2H_5) deposited as colorless needles, mp 145—147°. *Anal.* Calcd. for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.03; H, 7.20; N, 3.47. NMR ($CDCl_3$) δ: 4.34 (1H, d, C_1–H, J=8 Hz).

***cis*-5,6-Dibenzyloxy-2-ethylamino-1,2,3,4-tetrahydro-1-naphthalenol (10-*cis*: R=C_2H_5)**——To a suspension of $LiAlH_4$ (1.5 g) in THF (100 ml) was added **20**-*cis* (0.8 g) and the mixture was refluxed for 3.5 hr. After cooling, to the mixture was added 200 ml of ether, and the excess reagent and aluminum complex were decomposed by a dropwise addition of water. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. Recrystallization of the residue from ether afforded 0.35 g (50%) of **10**-*cis* (R=C_2H_5), as colorless powder, mp 115—117°. *Anal.* Calcd. for $C_{26}H_{29}NO_3 \cdot 1/2H_2O$: C, 75.70; H, 7.33; N, 3.40. Found: C, 76.07; H, 7.58; N, 3.46. NMR ($CDCl_3$–D_2O) δ: 4.54 (1H, d, C_1–H, J=4 Hz). Fumarate, mp 192—195° (dec.). *Anal.* Calcd. for $C_{26}H_{29}NO_3 \cdot 1/2C_4H_4O_4$: C, 72.86; H, 6.77; N, 3.04. Found: C, 73.05; H, 6.70; N, 2.93.

5,6-Dibenzyloxy-2-benzyloxycarbonylamino-1,2,3,4-tetrahydro-1-naphthalenol (14)——To a solution of **9**·TsOH (*cis*, *trans* mixture) (0.6 g) in AcOEt (30 ml) was added 3% aqueous K_2CO_3 (100 ml). To the mixture was added dropwise benzyloxycarbonyl chloride (1 g) with vigorous stirring. After stirring the mixture for 20 min under room temperature, AcOEt layer was separated, dried, and evaporated *in vacuo*. The residue was recrystallized from *n*-hexane–ether to give 0.4 g (70%) of **14** (*cis*, *trans* mixture) as colorless crystalline powder, mp 125—130°. *Anal.* Calcd. for $C_{31}H_{31}NO_5$: C, 74.83; H, 6.28; N, 2.82. Found: C, 75.34; H, 6.14; N, 2.71.

5,6-Dibenzyloxy-2-benzyloxycarbonylamino-3,4-dihydro-1(2*H*)-naphthalenone (15)——a) To a stirred solution of **14** (*cis*, *trans* mixture) (0.9 g) in acetone (50 ml) was added CrO_3–H_2SO_4 (Jones' reagent) under room temperature until the yellow color of the reagent was sustained. After the excess reagent was consumed by addition of MeOH, insoluble substance was filtered. The filtrate was poured into water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. To the residue was added ether (20 ml) to deposite 0.55 g (61%) of **15** as colorless crystals, mp 154—157°. *Anal.* Calcd. for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83. Found: C, 75.53; H, 5.83; N, 2.62.

b) To a stirred solution of **13** (0.4 g) in AcOEt (20 ml) was added dropwise benzyloxycarbonyl chloride (1 g) and subsequently 8% aqueous K_2CO_3 (50 ml) under room temperature. After stirring of the mixture for 15 min, the AcOEt layer was separated and the aqueous layer was extracted with AcOEt (20 ml). The combined AcOEt solution was dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ether–petroleum ether gave 0.46 g (87%) of **15** as colorless crystals, mp 154—157°, which showed complete identity with the sample prepared in a) in mixed mp and IR spectrum.

trans*-5,6-Dibenzyloxy-2-benzyloxycarbonylamino-1,2,3,4-tetrahydro-1-naphthalenol (14-*trans*)**——To a stirred solution of **15** (0.4 g) in MeOH (29 ml) was added portionwise $NaBH_4$ (1 g) at room temperature. After being stirred for further 15 min, the mixture was poured into water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ether gave 0.25 g (62%) of **14-*trans as colorless needles, mp 141—143°. *Anal.* Calcd. for $C_{31}H_{31}NO_5$: C, 74.83; H, 6.28; N, 2.82. Found: C, 75.26; H, 6.21; N, 2.70. NMR ($CDCl_3$) δ: 4.48 (1H, d, C_1-H, $J=7$ Hz).

2-Substituted Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (1) (Table I)——a) A solution of **4**·HBr (0.2 g) in 30—70% aqueous EtOH (15 ml) was subjected to catalytic reduction over PtO_2 (0.2 g) under atmospheric pressure and room temperature until absorption of hydrogen ceased. The catalyst was filtered, while the filtrate was dropped into ether (200 ml). To the ethereal solution was added EtOH until homogeneous clear solution was obtained. To this solution was added ether (500 ml) in small portions to deposit crystals of **1**·HBr. Derivatives **1d-*trans***, **1e**, and **1f** were prepared by this method.

b) A solution of **4**·HBr (0.2 g) in 5 ml of water was subjected to catalytic reduction over 5% Pd-C (0.2 g) under atmospheric pressure and room temperature until absorption of hydrogen ceased. After the catalyst was removed by filtration, the filtrate was lyophilized to give crystalline powder, which was recrystallized from EtOH–EtOAc to give **1**·HBr. Derivatives **1h** and **1i** were prepared by this method.

c) To a solution of 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol hydrobromide[2] (**1a**) (0.15 g) in EtOH (5—20 ml) was added an aldehyde (1—2 g). The mixture was subjected to catalytic reduction over 5% Pd–C (0.3—1 g) under atmospheric pressure and room temperature. After stoichiometric amount of hydrogen was absorbed, the catalyst was filtered, while the filtrate was dropped into 100—200 ml of ether. On standing the ethereal mixture overnight, **1**·HBr was deposited as colorless crystals. Derivatives **1j**, **1m**, **1s**, and **1t** were prepared by this method employing cyclohexanecarboxyaldehyde, 2-phenylpropanal, methoxyacetaldehyde and acrolein dimer, respectively, as the aldehyde. In the case of **1s**, the above procedure gave rise to a syrup, which was taken up in 0.5 ml of water and crystallized by adding in turn EtOH, AcOEt and ether.

d) To a solution of **1a**·HBr (0.4 g) in EtOH (20 ml) were added triethylamine (0.15 g) and a ketone (2 g) and the mixture was subjected to catalytic hydrogenation over 5% Pd-C (1 g) under atmospheric pressure and room temperature until stoichiometric amount of hydrogen was absorbed (24—72 hr). After removal of the catalyst by filtration, equivalent fumaric acid was added to the filtrate and the solution was evaporated *in vacuo*. Recrystallization of the residue from EtOH–AcOEt or aqueous acetone–ether afforded **1**·fumarate. By this method, derivatives **1n-*trans***, **1p-*trans*** and **1q** were prepared employing phenylacetone, *p*-methoxyphenylacetone, respectively, as the ketone.

e) A solution of 2-amino-5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone hydrobromide[2] (**5**) (0.3 g) in 50% EtOH (7 ml) was catalytically hydrogenated over PtO_2 (0.15 g) under atmospheric pressure and room temperature until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was added to a mixture of EtOH (10 ml), 10% Pd-C (0.5—2.0 g) and an aldehyde (3 g). The mixture was subjected to catalytic hydrogenation again until the absorption of hydrogen ceased. The catalyst was filtered, while the filtrate was dropped into ether (100 ml). To the mixture was added dropwise EtOH until clear homogeneous solution was obtained. Then 0.5—1 l of ether was added to the solution in small portions whereupon **1**·HBr was deposited as colorless crystals. Derivatives **1k**, **1l** and **1o** were prepared by this method employing respectively phenylacetaldehyde, 3-phenylpropanal and *p*-methoxyphenylacetaldehyde.

f) A solution of **9-*cis*** (0.4 g) in MeOH (15 ml) was subjected to catalytic hydrogenation over 10% Pd-C (0.7 g) under atmospheric pressure and room temperature. After removal of the catalyst by filtration, the filtrate was dropped into ether (500 ml) containing 1 ml of 47% HBr to deposit **1a-*cis***·HBr as colorless crystalline powder. Similarly, reduction of **9-*trans*** (0.75 g) over 10% Pd-C (0.3 g) afforded **1a-*trans***·HBr as colorless petals.

g) A solution of **14-*trans*** (0.4 g) in MeOH (10 ml) was catalytically hydrogenated over 10% Pd-C (0.2 g) under atmospheric pressure and room temperature. After addition of 0.5 ml of 47% HBr to the reaction mixture, the catalyst was filtered while the filtrate was added dropwise to 200 ml of ether to deposit crystals, which were collected by filtration and recrystallized from 80% aqueous MeOH (6 ml)–ether (200 ml) to give **1a-*trans***·HBr as colorless petals.

h) A solution of free base of **10,10-*cis***, or **10-*trans*** (0.4 g) in MeOH (10 ml) was catalytically hydrogenated over 5% Pd-C (0.2 g) under atmospheric pressure and room temperature. Removal of the catalyst followed by conversion to the hydrobromide or fumarate as described above afforded **1**. Derivatives **1c-*trans***, **1c-*cis***, **1g-*trans***, and **1g-*cis*** were thus prepared from the corresponding **10-*cis*** or **10-*trans*** derivatives. Derivative **1r-*trans*** was prepared from the corresponding **10**,[5] only the *trans* compound being separated on crystallization.

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