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The Synthesis of N,N′-Disubstituted 2,5-Diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol Derivatives

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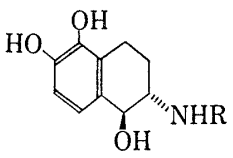
In a search for a new type of β-adrenoceptor agonist, a series of N,N′-disubstituted 2,5-diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**2a**—**q**), in which the 5-hydroxyl group of the previously reported rigid catecholamine (**1**) was replaced by methylamino, dimethylamino, ethylamino, dimethylamino, methanesulfonylamino, ureido, and formamido groups, were synthesized from 6-benzyloxy-5-nitro-4,3-dihydro-1(2*H*)-naphthalenone (**6**). 5-Chloro-2-isopropylamino derivative (**53**) was also prepared using an intermediate of those syntheses. Biological results for the two derivatives (**2d** and **2e**) are presented.

Keywords——tetrahydronaphthalene; tetrahydronaphthylamine; amino ethanol; rigid catecholamine derivative; Neber rearrangement; β-adrenoceptor agonist; β_2-selectivity

A series of our investigations on catecholamine derivatives revealed that *trans*-2-alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**) are excellent β-adrenoceptor agonists with considerable β_2-directing property[2-4] and that replacement of the 5-hydroxy group in **1** with other functional groups such as hydroxymethyl[5] and amino[6] groups has resulted in increased β_2-selectivity. On the other hand, recent studies in search for improved bronchodilators with better β_2-selectivity and longer duration of action have led to extensive modifications with respect to the *m*-hydroxyl group of adrenergic catecholamines. It has been reported that several *m*-amido derivatives as exemplified by soterenol (**3**),[7] carbuterol



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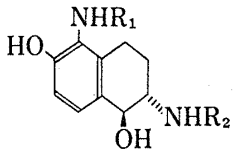

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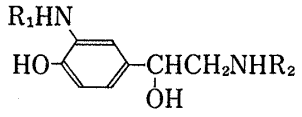


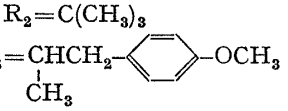
3: R_1=NHSO$_2$CH$_3$, R_2=CH(CH$_3$)$_2$
4: R_1=NHCONH$_2$, R_2=C(CH$_3$)$_3$
5: R_1=NHCHO, R_2= 

Chart 1

1) Location: *Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan.*
2) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
3) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **25**, 632 (1977).
4) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **25**, 2917 (1977).
5) H. Sugihara, K. Ukawa, H. Kuriki, M. Nishikawa, and Y. Sanno, *Chem. Pharm. Bull.* (Tokyo), **25**, 2988 (1977).
6) A. Miyake, H. Kuriki, N. Tada, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **25**, 3066 (1977).
7) K.W. Dungan, Y.W. Cho, A.W. Gomoll, D.M. Aviado, and P.M. Lish, *J. Pharmacol. Exp. Ther.*, **164**, 290 (1968).

(**4**),[8] BD-40A (**5**)[9] are the candidates for the improved bronchodilators. *m*-Alkylamino derivatives have also been shown to be potent β_2-agonists.[8] In view of this, attempts were made to synthesize N,N′-disubstituted 2,5-diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**2**) as an extension of our previous work.[6]

First the preparation of 5-methylamino derivatives (**2a—g**) was undertaken. Treatment of 6-benzyloxy-5-nitro-3,4-dihydro-1-(2*H*)-naphthalenone[6] (**6**) with Raney nickel and hydrazine in ethanol under reflux effected selective reduction of the nitro group to give 5-amino-6-benzyloxy derivative (**7**). Compound **7** was led to the N-trifluoroacetate (**8**) by treatment with trifluoroacetic anhydride. Methylation of **8** with methyl iodide followed by alkaline hydrolysis afforded 5-methylamino derivative (**9**). Since our experience during the investigations of this series suggested that Neber rearrangement of an oxime tosylate of 1-tetralone derivative into an α-amino ketone might be interfered by the presence of an NH or OH group in the molecule, the NH group at the 5-position was protected with a benzyl group prior to the rearrangement. Thus, **9** was allowed to react with benzyl chloride to give 5-benzylmethylamino tetralone (**10**), which was led to the tosylate (**12**) *via* the oxime (**11**). Compound **12** was subjected to Neber rearrangement by treatment with potassium

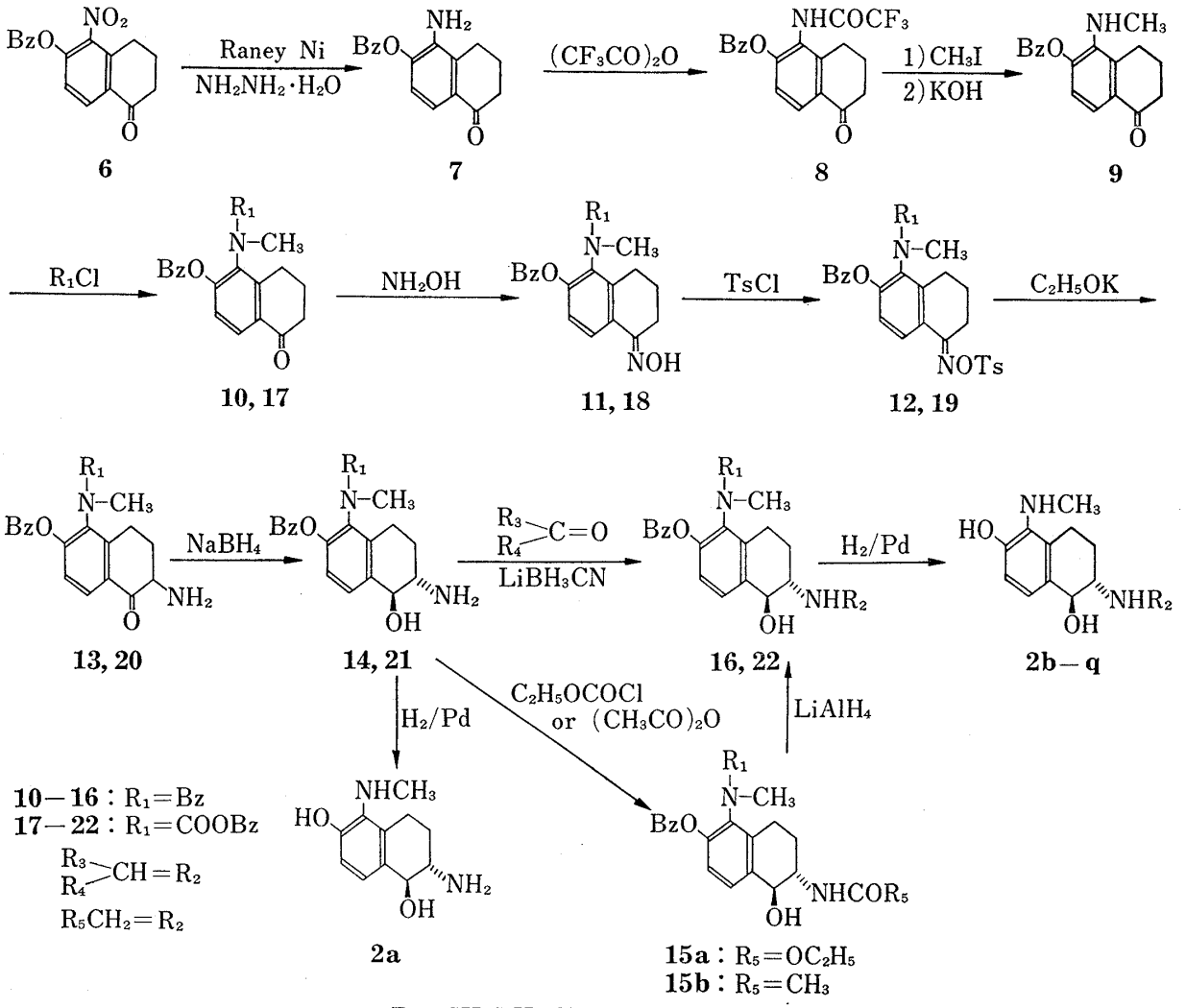
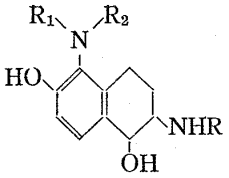
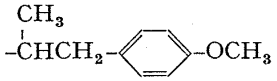


Chart 2

8) C. Kaiser, D.F. Colella, M.S. Schartz, E. Garvey, and J.R. Wardell, Jr., *J. Med. Chem.*, **17**, 49 (1974).
9) H. Ida, *Arzneim.-Forsch.*, **26**, 839 (1976).

Table I. N,N′-Substituted 2,5-Diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (2)



Compound No.	$N\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$	R	Configulation at C_1–C_2	Salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	$NHCH_3$	H	*trans*	HCl	65	300	$C_{11}H_{16}N_2O_2 \cdot 2HCl \cdot H_2O$	44.15 (44.46)	6.74 (6.61)	9.36 (9.29)
2b	$NHCH_3$	CH_3	*trans*	Fumarate	72	148—150	$C_{12}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 3/2H_2O$	52.59 (52.33)	6.89 (6.83)	7.67 (7.35)
2c	$NHCH_3$	C_2H_5	*trans*	Fumarate	60	187—189	$C_{13}H_{20}N_2O_2 \cdot C_4H_4O_4$	57.94 (57.66)	6.87 (6.75)	7.95 (7.81)
2d	$NHCH_3$	$CH(CH_3)_2$	*trans*	Fumarate	75	174—176	$C_{14}H_{22}N_2O_2 \cdot C_4H_4O_4$	59.00 (59.24)	7.15 (7.16)	7.65 (7.92)
2e	$NHCH_3$		*trans*	Fumarate	80	196—198	$C_{15}H_{22}N_2O_2 \cdot 1/2C_4H_4O_4 \cdot 1/2H_2O$	61.98 (62.00)	7.56 (7.85)	8.51 (8.28)
2f	$NHCH_3$		*trans*	HCl	83	218—220	$C_{17}H_{26}N_2O_2 \cdot 2HCl$	56.20 (56.16)	7.77 (7.81)	7.71 (7.55)
2g	$NHCH_3$		*trans*	HCl	75	216—218	$C_{21}H_{27}N_2O_3 \cdot 2HCl$	58.88 (58.70)	6.82 (6.86)	6.54 (6.41)
2h	$N(CH_3)_2$	$CH(CH_3)_2$	*trans*	HCl	70	220—222	$C_{15}H_{24}N_2O_2 \cdot 2HCl$	53.41 (53.25)	7.77 (7.83)	8.31 (8.29)
2i	NHC_2H_5	$CH(CH_3)_2$	*trans*	HCl	64	198—200	$C_{15}H_{24}N_2O_2 \cdot 2HCl \cdot 1/2H_2O$	52.02 (52.09)	7.86 (7.90)	8.09 (7.62)
2j	$N(C_2H_5)_2$	$CH(CH_3)_2$	*trans*	Fumarate	77	215—217	$C_{17}H_{28}N_2O_2 \cdot C_4H_4O_4$	61.74 (61.73)	7.90 (8.10)	6.86 (7.14)
2k	$NHSO_2CH_3$	H	*trans*	HCl	47	233—235	$C_{11}H_{16}N_2O_4S \cdot HCl \cdot H_2O$	40.43 (40.87)	5.86 (5.74)	8.57 (8.48)
2l	$NHSO_2CH_3$	$CH(CH_3)_2$	*trans*	HCl	56	210—213	$C_{14}H_{22}N_2O_4S \cdot HCl$	47.93 (47.63)	6.61 (6.81)	7.99 (7.74)
2m	$NHCONH_2$	CH_3	*cis*	HCl	59	amorphous	$C_{12}H_{17}N_3O_2S \cdot HCl \cdot H_2O$	47.13 (47.36)	6.59 (6.44)	13.74 (13.42)
2n	$NHCONH_2$	CH_3	*trans*	HCl	63	amorphous	$C_{12}H_{17}N_3O_2 \cdot HCl \cdot H_2O$	47.13 (47.02)	6.59 (6.32)	13.74 (13.43)
2o	$NHCONH_2$	$CH(CH_3)_2$	*trans*	HCl	31	198—200	$C_{14}H_{21}N_3O_3 \cdot HCl$	53.24 (53.21)	7.02 (7.01)	13.31 (13.50)
2p	NHCHO	CH_3	*cis*	Fumarate	70	198—201	$C_{12}H_{16}N_2O_3 \cdot C_4H_4O_4$	54.54 (54.33)	5.72 (6.02)	7.95 (7.95)
2q	NHCHO	CH_3	*trans*	Fumarate	72	160—163	$C_{12}H_{16}N_2O_3 \cdot 1/2C_4H_4O_4 \cdot 1/2H_2O$	55.43 (55.49)	6.31 (6.07)	9.24 (9.01)

ethoxide and the resulting amino ketone (**13**) was reduced with sodium borohydride ($NaBH_4$) without purification to afford *trans*-2-amino-6-benzyloxy-5-benzylmethylamino-1,2,3,4-tetrahydro-1-naphthalenol (**14**)[10] in 17% yield from **12**. The poor yield of **14** was presumed to be due to the low yield in the Neber rearrangement, since the $NaBH_4$ reduction of carbonyl group in the analogous compounds had proceeded almost quantitatively.

Assuming that the basicity of the benzylmethylamino group might have some influence on the delicate reaction condition required for the rearrangement, similar procedures were conducted employing benzyloxycarbonyl group as the protecting group of the methylamino moiety. Thus, **9** was acylated with benzoyloxycarbonyl chloride in the presence of potassium carbonate to give N-benzyloxycarbonyl-N-methylamino tetralone (**17**), which was led to oxime (**18**) and then to the tosylate (**19**). Neber rearrangement of **19** into amino ketone (**20**) followed by reduction with $NaBH_4$ under similar conditions afforded *trans*-amino alcohol (**21**) in a slightly improved yield of 28% from **19**.

Compounds **14** and **21** were led to the corresponding 2-alkylamino derivatives (**16** and **22**) by the reductive alkylation with a variety of ketones[11] and lithium cyanoborohydride ($LiBH_3CN$).[12] The 2-methylamino and 2-ethylamino derivatives (**16**: R_2=CH_3 and C_2H_5) were prepared by lithium alminum hydride ($LiAlH_4$) reduction of 2-ethoxycarbonylamino and 2-acetamido derivatives (**15a** and **15b**) which were derived from **14** by acylation with ethyl chloroformate and acetic anhydride, respectively. Catalytic hydrogenation of **16**, **21** and **22**

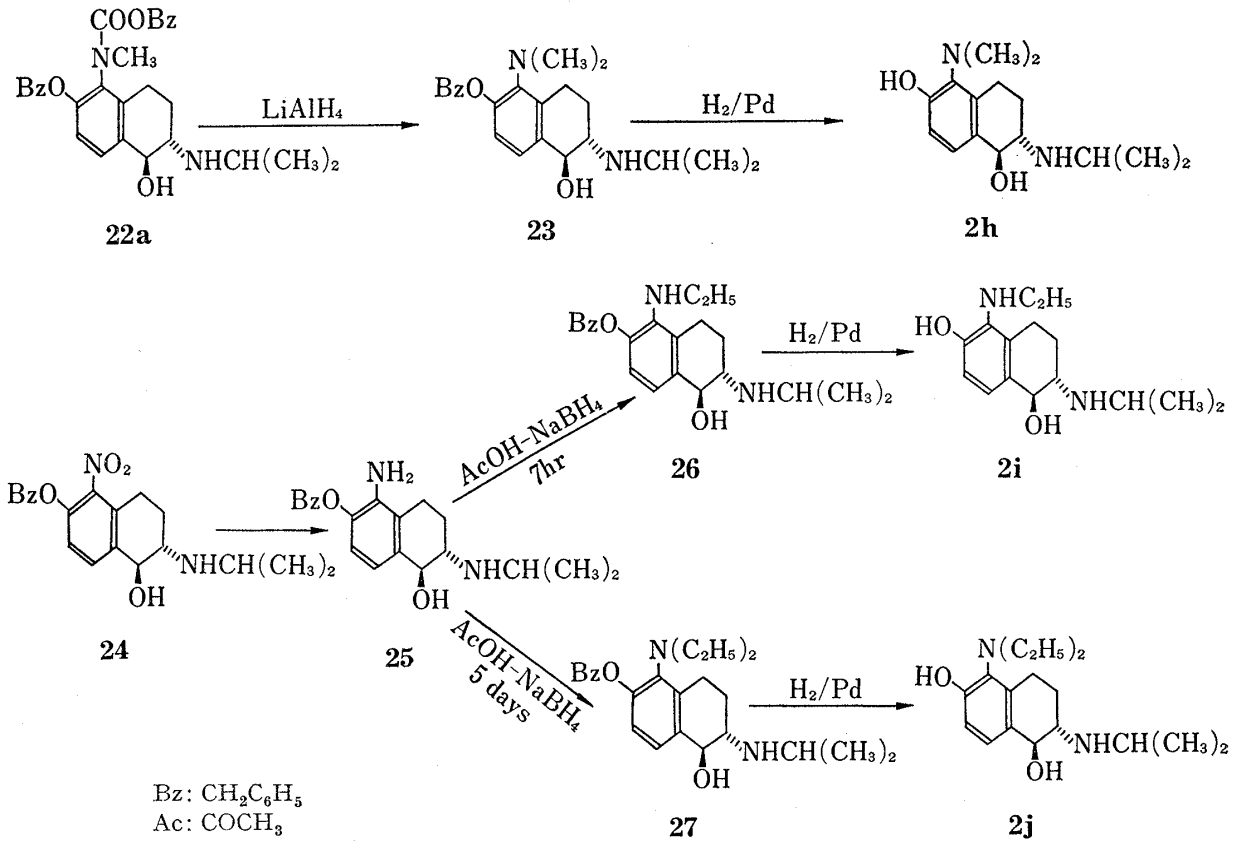


Chart 3

10) Configurations of the substituents at C_1–C_2 in the 2-amino-1,2,3,4-tetrahydro-1-naphthalenol derivatives were determined on the basis of the nuclear magnetic resonance (NMR) spectra,[3–6] which showed coupling constant (J) of 8—10 Hz for the 1,2-*trans* isomers and 0—3 Hz for the *cis* isomers.

11) Although in the case of **22d** asymmetric induction might have arisen at the α-carbon in R_2 owing to the two asymmetric centers at the 1- and 2-positions in **21**, we have no evidence at present concerning the stereochemistry of the substituent R_2 in **22d** (Table V) and hence R in **2g** (Table I).

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

over palladium-charcoal effected simultaneous removal of the two benzyl groups in the 5- and 6-substituents to afford expected *trans*-2-amino-6-hydroxy-5-methylamino-1,2,3,4-tetrahydro-1-naphthalenol derivatives (**2a**—**g**) (Table I).

Since biological tests of the obtained compounds revealed an excellent β_2-adrenoceptor agonistic activity of **2d**, the synthetic work was extended further to the preparation of 5-dimethylamino, ethylamino and diethylamino derivatives (**2h**, **2i**, and **2j**). Thus, compound **22a** (**22**: R_2=$CH(CH_3)_2$) was reduced with $LiAlH_4$ to give 6-benzyloxy-5-dimethylamino derivative (**23**), debenzylation of which by catalytic hydrogenation afforded **2h**. On the other hand, *trans*-6-benzyloxy-2-isopropylamino-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**24**)[6] was treated with Raney nickel-hydrazine to give the corresponding 5-amino derivative (**25**). Compound **25** was allowed to react with $NaBH_4$ in acetic acid[13] at room temperature. Work-up of the reaction mixture after seven hours afforded 5-ethylamino derivative (**26**), while prolonged standing of the mixture for five days gave rise to additional N-ethylation to give 5-diethylamino derivative (**27**). Compounds **26** and **27** were catalytically hydrogenated to afford **2i** and **2j**, respectively.

Subsequently, efforts were directed towards the synthesis of 5-acylamino derivatives. Compound **7** was acylated with methanesulfonyl chloride to give 6-benzyloxy-5-methanesulfonylamino-3,4-dihydro-1(2*H*)-naphthalenone (**28**). It was found, however, that the

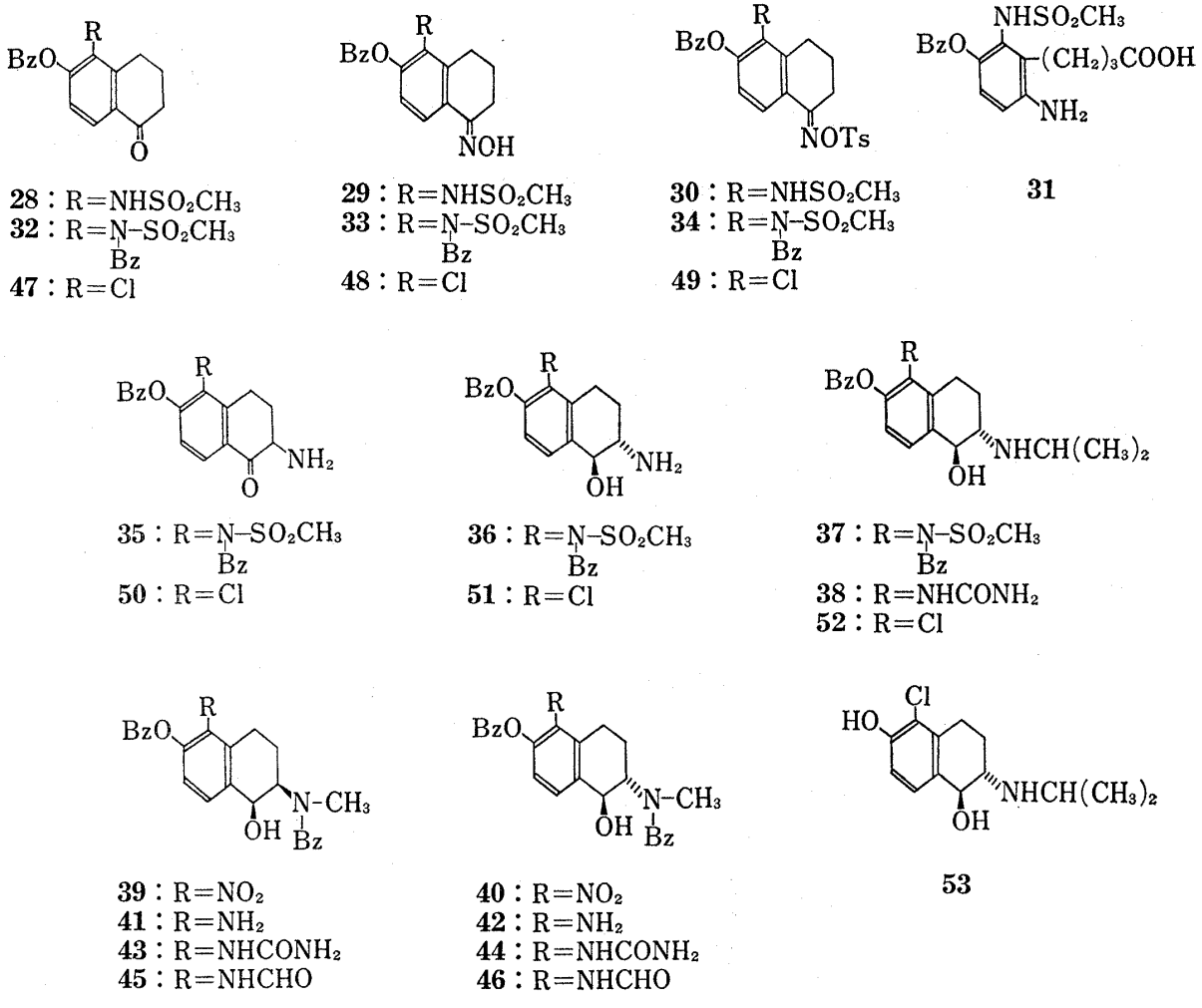


Chart 4

13) G.W. Gribble, P.D. Lord, J.S. Stephen, J.T. Eaton, and J.L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).

tosylate (**30**) prepared from **28** *via* oxime (**29**) failed to undergo Neber rearrangement into the expected α-amino ketone, affording 3-(6-amino-3-benzyloxy-2-methanesulfonylaminophenyl)butyric acid (**31**) presumably as a result of Beckmann-type rearrangement. The Neber rearrangement was ultimately achieved by masking the NH group with a benzyl group for the same reason as mentioned above. Thus, benzylation of **28** with benzylchloride to afford N-benzylmethanesulfonylaminotetralone (**32**) followed by oxime formation, O-tosylation and the rearrangement with potassium ethoxide gave α-aminoketone (**35**) *via* compounds **33** and **34**. Reduction of **35** with $NaBH_4$ have *trans*-amino alcohol (**36**), catalytic hydrogenation of which over palladium-charcoal afforded *trans*-2-amino-6-hydroxy-5-methanesulfonylamino-1,2,3,4-tetrahydro-1-naphthalenol (**2k**). N-Alkylation of **36** followed by removal of the two benzyl groups by catalytic hydrogenation gave the corresponding 2-isopropylamino derivative (**2l**). On the other hand, 2-isopropylamino-5-ureido derivative (**2o**) was obtained from **25** by the reaction with potassium cyanate to give **38** and the subsequent catalytic hydrogenation.

Two pairs of *cis*- and *trans*-isomers of 5-ureido- and 5-formamido-2-methylamino derivatives (**2m**, **2n** and **2p**, **2q**) were prepared from *cis*- and *trans*-2-(N-benzyl-N-methylamino)-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**39** and **40**).[6] The nitro groups of **39** and **40** were reduced with Raney nickel-hydrazine to give 5-amino derivatives (**41** and **42**), which were led to 5-ureido derivatives (**43** and **44**) and 5-formamido derivatives (**45** and **46**) by the reaction with potassium cyanate and formic acid-acetic anhydride, respectively. Removal of the N- and O-benzyl groups of compounds **43**, **44**, **45** and **46** afforded **2m**, **2n**, **2p** and **2q**, respectively (Table I).

Since biological results obtained during our investigations[5,6] seemed to suggest that introduction of a group having considerable bulkiness and electron negativity at the 5-position might be a requisite for β_2-adrenoceptor activity, the synthesis of 5-chloro-6-hydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (**53**), the 5-chloro analog of **1**, was subsequently undertaken employing compound **7** as the starting material. Diazotization of **7** followed by treatment with cuprous chloride in hydrochloric acid gave 6-benzyloxy-5-chloro tetralone (**47**). Compound **47** was led to **53** by a sequence of reactions similarly to the cases in the above-mentioned 5-substituted amino derivatives, *i.e.*, oxime formation, O-tosylation, Neber rearrangement to α-amino ketone, $NaBH_4$ reduction of the 1-carbonyl group, N-isopropylation and debenzylation by catalytic hydrogenation *via* compounds **48**, **49**, **50**, **51**, and **52**.

The β_1- and β_2-adrenoceptor activities of some of the obtained derivatives were measured *in vitro* using isolated arterial preparations and tracheal strips of guinea pig, respectively according to the methods described in a foregoing paper.[2] Table II shows the biological results of two compounds, **2d** and **2e**, which have been examined in some detail.

Table II. β-Adrenoceptor Activity of 2-Substituted Amino-6-hydroxy-5-methylamino-1,2,3,4-tetrahydro-1-naphthalenol

Compound	Isolated atria (β_1)			Isolated tracheal strip (β_2)			Separation ratio[d]
	n[a]	PD_2[b]	i.a.[c]	n	PD_2[b]	i.a.	
2d	4	6.62±0.44	0.75	4	7.98±0.05	1.0	23.0
2e	4	8.06±0.32	0.8	4	8.66±0.08	1.0	4.0
l-Isoproterenol	8	8.67±0.09	1.0	8	8.02±0.11	1.0	0.22

a) Number of experiments. b) Mean±S.E. c) Intrinsic activity. d) β_1/β_2.

Experimental[14]

5-Amino-6-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (7)——A solution of 6-benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**6**)[6] (18 g) in EtOH (240 ml) was refluxed with stirring, while to the solution were added Raney Ni (2.0 g) and then dropwise a solution of 100% $NH_2NH_2 \cdot H_2O$ (14 g) in EtOH (30 ml) over a period of 1 hr. After the mixture was refluxed for further 30 min, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to 100 ml. Filtration of the resulting precipitate and recrystallization from EtOH gave **7** (14 g, 87%) as colorless needles, mp 124—126°. *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.07; H, 6.34; N, 4.98. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3400 (NH_2), 1675 (C=O). NMR (in $CDCl_3$) δ: 5.16 (2H, s, $CH_2C_6H_5$), 6.83 (1H, d, $J=8$ Hz, aromatic-H), 7.46 (1H, d, $J=8$ Hz, aromatic-H).

6-Benzyloxy-5-trifluoroacetylamino-3,4-dihydro-1(2*H*)-naphthalenone (8)——To a stirred solution of **7** (25 g) in $CHCl_3$ (200 ml) was added dropwise $(CF_3CO)_2O$ (30 g). The mixture was stirred at room temperature for 2 hr and poured into water (200 ml). The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. Recrystallization of the residue from MeOH gave **8** (30 g, 87%) as colorless needles, mp 190—191°. *Anal.* Calcd. for $C_{19}H_{16}F_3NO_3$: C, 62.80; H, 4.44; N, 3.86. Found: C, 62.77; H, 4.15; N, 3.74. IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH), 1700 (C=O).

6-Benzyloxy-5-methylamino-3,4-dihydro-1(2*H*)-naphthalenone Hydrochloride (9)——To a solution of **8** (25 g) in acetone (100 ml) was added KOH (16 g), and the mixture was refluxed with stirring for 30 min. After dropwise addition of CH_3I (41 g) to the mixture, the mixture was refluxed for 2 hr and evaporated *in vacuo*. To a solution of the residue in 50% EtOH (500 ml) was added KOH (25 g) and the mixture was refluxed with stirring for 2 hr. The reaction mixture was poured into ice-water (250 ml) and extracted with AcOEt (500 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 20% ethanolic HCl (150 ml) and allowed to stand at room temperature for 2 hr. The resulting precipitate was collected by filtration to give **9**·HCl (18 g, 84%) as colorless needles, mp 194—195°. *Anal.* Calcd. for $C_{18}H_{19}NO_2 \cdot HCl \cdot 1/2H_2O$: C, 66.15; H, 6.17; N, 4.29. Found: C, 66.31; H, 6.17; N, 4.12. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR (in d_6-DMSO) δ: 2.84 (3H, s, N–CH_3).

5-Benzylmethylamino-6-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (10)——A mixture of **9** (31 g), K_2CO_3 (14 g), KI (2.0 g) and benzyl chloride (18 g) in EtOH (200 ml) was stirred at 80° for 5 hr. After cooling, the mixture was poured into water (500 ml) and extracted with AcOEt (1 l). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 20% ethanolic HCl (50 ml), diluted with ether (50 ml) and allowed to stand at room temperature. The resulting precipitate was filtered to give **10**·HCl (40 g, 99%) as colorless needles, mp 157—159°. *Anal.* Calcd. for $C_{22}H_{25}NO_2 \cdot HCl$: C, 73.60; H, 6.43; N, 3.44. Found: C, 73.54; H, 6.30; N, 3.25.

6-Benzyloxy-5-(N-benzyloxycarbonyl-N-methyl)amino-3,4-dihydro-1(2*H*)-naphthalenone (17)——To a stirred suspension of **9** (25 g) and K_2CO_3 (25 g) in a mixture of $CHCl_3$ (300 ml) and water (300 ml) was added dropwise benzyloxycarbonyl chloride (19 g). After stirring at room temperature for 5 hr, the mixture was allowed to stand overnight. The organic layer was separated dried, over Na_2SO_4 and evaporated *in vacuo* to give **17** (35 g, 98%) as a colorless oil. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1670 (C=O). NMR (in $CDCl_3$) δ: 3.12 (3H, s, N–CH_3), 5.02 (4H, m, $CH_2C_6H_5 \times 2$).

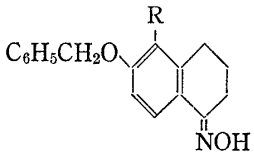
6-Benzyloxy-5-methanesulfonylamino-3,4-dihydro-1(2*H*)-naphthalenone (28)——To a stirred solution of **7** (13 g) in pyridine (100 ml) was added CH_3SO_2Cl (6.0 g). After stirring at room temperature for 3 hr, the mixture was poured into water (100 ml). The resulting precipitate was filtered, washed with water and recrystallized from EtOH to give **28** (15 g, 90%) as colorless needles. mp 184—185°. *Anal.* Calcd. for $C_{18}H_{19}NO_4S$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.57; H, 5.54; N, 3.89. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1675 (C=O). NMR (in $CDCl_3$) δ: 2.88 (3H, s, CH_3), 5.17 (2H, s, CH_2–C_6H_5).

6-Benzyloxy-5-(N-benzyl-N-methanesulfonyl)amino-3,4-dihydro-1(2*H*)-naphthalenone (32)——A mixture of **28** (36 g), K_2CO_3 (9.0 g), KI (2.0 g) and benzyl chloride (18 g) in dimethyl formamide (DMF) (200 ml) was heated at 100° with stirring for 2 hr. After cooling, the mixture was poured into water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from EtOH to give **32** (37 g, 87%) as pale yellow prisms, mp 206—208°. *Anal.* Calcd. for $C_{25}H_{25}NO_4S$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.65; H, 5.71; N, 3.01.

6-Benzyloxy-5-chloro-3,4-dihydro-1(2*H*)-naphthalenone (47)——To a solution of **7** (14 g) in a mixture of DMF (100 ml) and conc. HCl (22 ml) was added dropwise a solution of $NaNO_2$ (3.5 g) in water (10 ml) with stirring at 0°. The resulting solution of the diazonium compound was added dropwise to a stirred solution of CuCl(7.0 g) in conc. HCl (22 ml) at 0°. After the addition was completed, the solution was stirred at room temperature for 1 hr. The mixture was poured into water (500 ml) and extracted with AcOEt (500 ml).

14) All melting points were taken on a Kofler-type hot-stage apparatus (Yanagimito Co.) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on Varian HA-100 or A-60 high resolution spectrometers. Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. The mass spectra were determined on Hitachi RMU-6D mass spectrometer.

Table III. 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime



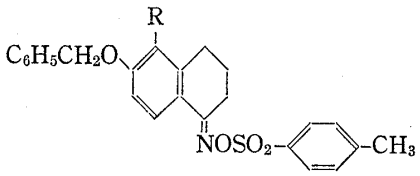
Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
11	$-\overset{\overset{CH_3}{\vert}}{N}-CH_2C_6H_5$	97	114—115	$C_{26}H_{26}N_2O_2$	77.69 (77.67)	6.78 (6.96)	7.25 (7.30)
18	$-\overset{\overset{CH_3}{\vert}}{N}-COOCH_2C_6H_5$	85	Oil	$C_{27}H_{26}N_2O_4$	—	—	—
29	$-NHSO_2CH_3$	85	221—223	$C_{18}H_{20}N_2O_4S$	59.99 (60.32)	5.59 (5.44)	7.77 (7.70)
33	$-\overset{\overset{SO_2CH_3}{\vert}}{N}-CH_2C_6H_5$	99	223—225	$C_{25}H_{26}N_2O_4S$	66.65 (66.65)	5.82 (5.66)	6.22 (6.23)
48	Cl	75	175—176	$C_{17}H_{16}ClNO_2$	67.66 (67.59)	5.35 (5.73)	4.64 (4.35)

The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. Column chromatography of the residue on silica gel using benzene as the eluant afforded **47** (4.0 g, 27%) as colorless leaflets. mp 99—100°. *Anal.* Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27. Found: C, 71.33; H, 4.83. IR ν_{max}^{Nujol} cm^{-1}: 1675 (C=O). NMR (in $CDCl_3$) δ: 5.18 (2H, s, $CH_2C_6H_5$), 6.80 (1H, d, $J=10$ Hz, aromatic-H), 7.90 (1H, d, $J=10$ Hz, aromatic-H).

5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime (11, 18, 29, 33 and 48) (Table III)——General Procedure: To a solution of a naphthalenone (**10**, **17**, **28**, **32** or **47**) (0.1 mol) in MeOH (300 ml) and water (30 ml) were added K_2CO_3 (0.2 mol) and $NH_2OH \cdot HCl$ (0.4 mol). The mixture was refluxed for 1.5—3 hr with stirring. After cooling, the mixture was poured into water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from MeOH to give the oxime. Compound **18** was obtained as an oil, which was used for the subsequent step without purification.

5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-*p*-Toluenesulfonate (12, 19, 30, 34 and 49) (Table IV)——General Procedure: To a stirred solution of an oxime (**11**, **18**, **29**, **33** or **48**) (0.1 mol)

Table IV. 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-*p*-Toluenesulfonate



Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
12	$-\overset{\overset{CH_3}{\vert}}{N}-CH_2C_6H_5$	87	Oil	$C_{32}H_{32}N_2O_4S$	—	—	—
19	$-\overset{\overset{CH_3}{\vert}}{N}-COOCH_2C_6H_5$	93	158—160	$C_{33}H_{32}N_2O_6S$	67.80 (67.74)	5.52 (5.47)	4.79 (4.60)
30	$-NHSO_2CH_3$	75	166—168	$C_{25}H_{26}N_2O_6S_2$	58.36 (58.48)	5.09 (4.93)	5.45 (5.54)
34	$-\overset{\overset{SO_2CH_3}{\vert}}{N}-CH_2C_6H_5$	94	159—161	$C_{32}H_{32}N_2O_6S_2$	63.57 (63.54)	5.34 (5.38)	4.63 (4.54)
49	Cl	96	153—155	$C_{24}H_{22}ClNO_4S$	63.23 (63.11)	4.87 (4.63)	3.07 (2.99)

in pyridine (100 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (0.2 mol) in pyridine (50 ml) at 5°. After the addition was completed, the mixture was stirred at room temperature for 3—5 hr, and then poured into ice-water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from benzene to give the oxime *p*-toluesulfonate.

2-Amino-6-(N-benzyl-N-methanesulfonyl)amino-6-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (35)——To a stirred solution of **34** (24 g) in dry benzene (400 ml) was added dropwise under nitrogen a chilled solution of KOEt prepared from K (1.7 g) and abs. EtOH (50 ml), keeping the reaction temperature at 5°. After the addition was completed, the reaction mixture was stirred for further 3 hr and allowed to stand overnight in a refrigerator. The deposited insoluble substance was removed by filtration, and to the filtrate was added 10% HCl (80 ml). The resulting crystals were collected by filtration and dissolved in EtOH (200 ml). The solution was decolorized with activated charcoal, concentrated to 50 ml and diluted with ether (100 ml) to deposit **35**·HCl (6.0 g, 31%) as colorless needles, mp 193—195°. *Anal.* Calcd. for $C_{25}H_{26}N_2O_4S$·HCl: C, 61.66; H, 5.59; N, 5.75. Found: C, 61.78; H, 5.57; N, 5.60.

2-Amino-6-benzyloxy-5-chloro-3,4-dihydro-1(2*H*)-naphthalenone (50)——To a stirred solution of **49** (5.2 g) in dry benzene (100 ml) was added dropwise a chilled solution of KOEt, prepared from K (0.53 g) and abs. EtOH (16 ml), at 5° under nitrogen. After the addition was completed, the mixture was stirred for 3hr and allowed to stand for 5 days in a refrigerator. After the insoluble substance was removed by filtration, the filtrate was extracted with 10% HCl (100 ml) and evaporated *in vacuo* below 40°. The residue was taken up in MeOH (100 ml) and treated with decolorizing charcoal. After being concentrated to 20 ml *in vacuo*, the solution was diluted with ether (100 ml) to deposit **50**·HCl (1.0 g, 26%) as colorless needles, mp 251—253°. *Anal.* Calcd. for $C_{17}H_{16}ClNO_2$·HCl: C, 60.36; H, 5.07; N, 4.14. Found: C, 59.98; H, 4.94; N, 4.36.

4-(6-Amino-3-benzyloxy-2-methanesulfonylaminophenyl)butyric Acid (31)——To a stirred solution of **30** (2.0 g) in dry benzene (100 ml) was added dropwise a chilled solution of KOEt, prepared from K (0.33 g) and abs. EtOH (10 ml), at 5° under nitrogen. After the addition was completed, the mixture was stirred for 1 hr and allowed to stand overnight in a refrigerator. After the insoluble substance was removed by filtration, the filtrate was extracted with 10% HCl (20 ml) and evaporated *in vacuo* below 40°. The residue was taken up in EtOH (100 ml) and treated with activated charcoal. After being concentrated to 10 ml *in vacuo*, the solution was diluted with ether (20 ml) to deposit **31**·HCl (0.7 g, 45%) as colorless needles, mp 172—175°. *Anal.* Calcd. for $C_{17}H_{20}N_2O_5S$·HCl: C, 50.94; H, 5.28; N, 6.99. Found: C, 50.88; H, 5.21; N, 6.67.

***trans*-2-Amino-5-benzylmethylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol(14)**——To a stirred solution of **12** (24 g) in dry benzene (400 ml) was added dropwise a chilled solution of KOEt in EtOH, prepared from K (3.9 g) and abs. EtOH (100 ml). After the addition was completed, the mixture was stirred for 3 hr and allowed to stand overnight in a refrigerator. The insoluble substance was removed by filtration and the filtrate was extracted with 10% HCl (200 ml). The extract was decolorized with activated charcoal and evaporated *in vacuo* to give **13**·HCl as a brown syrup, which was taken up in MeOH (200 ml). To the solution was added portionwise $NaBH_4$ (10 g) with stirring under ice-cooling. After the stirring was continued for additional 30 min, the mixture was poured into ice-water (500 ml) and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. After the residue was taken up in MeOH (50 ml) and treated with charcoal, saturated ethereal solution of oxalic acid (50 ml) was added to the solution and the mixture was allowed to stand overnight in a refrigerator. Filtration of the resulting crystals gave **14** oxalate (4.6 g, 17%) as colorless needles, mp 189—191°. *Anal.* Calcd. for $C_{25}H_{28}N_2O_2 \cdot C_2H_2O_4$: C, 67.76; H, 6.32; N, 5.86. Found: C, 67.55; H, 6.10; N, 5.73. NMR (in d_6-DMSO) δ: 4.60 (1H, d, J=10 Hz, C_1–H).

***trans*-2-Amino-5-(N-benzyloxycarbonyl-N-methyl)amino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (21)**——To a stirred solution of **19** (16 g) in dry benzene (300 ml) was added dropwise a chilled solution of KOEt, prepared from K (1.3 g) and abs. EtOH (39 ml). After the addition was completed, the reaction mixture was stirred for further 5 hr, and then allowed to stand for 5 days in a refrigerator. After insoluble substance was removed by filtration, the filtrate was extracted with 10% HCl (200 ml). The extract was treated with activated charcoal and evaporated to dryness *in vacuo* to give crude **20**·HCl as brown syrup, which was taken up in MeOH (100 ml). To the solution was added, in portions, $NaBH_4$ (5.0 g) with stirring under ice-cooling. After 30 min, the mixture was poured into ice-water (500 ml) and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give an oil which was dissolved in ethanolic HCl (100 ml). After treatment with charcoal, the solution was condensed to 50 ml and then diluted with ether (100 ml). Filtration of the resulting crystals gave **21**·HCl (3.3 g, 28%) as colorless needles, mp 145—147°. *Anal.* Calcd. for $C_{26}H_{28}N_2O_4$·HCl: C, 66.58; H, 6.23; N, 5.98. Found: C, 66.42; H, 6.01; N, 5.66. NMR (in d_6-DMSO) δ: 4.58 (1H, d, J=10 Hz, C_1–H).

***trans*-2-Amino-5-(N-benzyl-N-methanesulfonyl)amino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (36)**——To a stirred solution of **35**·HCl (6.0 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (3.0 g) at 5°. After stirring for further 30 min, the mixture was poured into ice-water (300 ml) and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in ethanolic HCl (10 ml) and diluted with ether (50 ml). The resulting precipitate was collected by filtration

to give **36**·HCl (5.0 g, 83%) as colorless needles, mp 205—207°. *Anal.* Calcd. for $C_{25}H_{28}N_2O_4S$·HCl: C, 61.40; H, 5.98; N, 5.73. Found: C, 60.96; H, 5.96; N, 5.72. NMR (in d_6-DMSO) δ: 4.65 (1H, d, J=10 Hz, C_1–H).

***trans*-2-Amino-6-benzoyloxy-5-chloro-1,2,3,4-tetrahydro-1-naphthalenol (51)**——To a stirred solution of **50** (7.0 g) in MeOH (140 ml) was added portionwise $NaBH_4$ (3.5 g) at 5°. After stirring for further 30 min, the mixture was poured into ice-water (300 ml) and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved into ethanolic HCl (50 ml) and then diluted with ether (100 ml). The resulting crystals were filtered to give **51**·HCl (5.0 g, 71%) as colorless needles, mp 277—279°. *Anal.* Calcd. for $C_{17}H_{18}ClNO_2$·HCl: C, 60.01; H, 5.63; N, 4.12. Found: C, 60.41; H, 5.41; N, 4.10. NMR (in d_6-DMSO) δ: 4.85 (1H, d, J=8 Hz, C_1–H).

***trans*-5-Benzylmethylamino-6-benzyloxy-2-ethoxycarbonylamino-1,2,3,4-tetrahydro-1-naphthalenol (15a)**——To a stirred solution of **14** oxalate (2.0 g) and K_2CO_3 (2.0 g) in a mixture of $CHCl_3$ (50 ml) and water (50 ml) was added dropwise ethoxycarbonyl chloride (2.0 g). After stirring for 2 hr at room temperature, the organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from ether–petr. ether to give **15a** (1.5 g, 79%) as colorless needles, mp 119—120°. *Anal.* Calcd. for $C_{28}H_{32}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.66; H, 6.00; N, 6.07. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR (in d_6-DMSO) δ: 1.23 (3H, t, J=6 Hz, CH_3), 2.60 (3H, s, N–CH_3), 4.43 (1H, d, J=8 Hz, C_1–H).

***trans*-2-Acetylamino-5-benzylmethylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (15b)**——Free base of **14**, which was prepared by neutralization **14** oxalate (2.0 g) with $NaHCO_3$ followed by extraction with $CHCl_3$ and evaporation, was dissolved in MeOH (50 ml). To the solution was added dropwise Ac_2O (10 ml) with stirring at room temperature. After stirring for further 3 hr, the mixture was poured into water (200 ml) and extracted with AcOEt (200 ml). The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was triturated with ether and recrystallized from AcOEt to give **15b** (1.4 g, 79%) as colorless needles, mp 125—127°. *Anal.* Calcd. for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02; N, 6.51. Found: C, 75.41; H, 7.50; N, 6.65. IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). NMR (in d_6-DMSO): 1.90 (3H, s, CH_3), 2.60 (3H, s, N–CH_3), 4.60 (1H, d, J=8 Hz, C_1–H).

***trans*-2-Substituted Amino-6-benzyloxy-5-substituted-1,2,3,4-tetrahydro-1-naphthalenols (Table V)**——a) General Procedure: To a stirred solution of *trans*-2-amino-6-benzyloxy-5-substituted-1,2,3,4-tetrahydro-1-naphthalenol hydrochloride (**14**, **21**, **36** or **51**) (1.0 g) in MeOH (30 ml) was added a ketone (3—5 g) and $LiBH_3CN$·2 dioxane[11] (1.0 g) under ice-cooling. After being stirred for 5—12 hr at room temperature, the mixture was poured into ice-water (100 ml) and acidified with 10% HCl. The solution was neutralized with $NaHCO_3$ and extracted with AcOEt (300—500 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give free base of the objective compound, which was converted to the hydrochloride or the oxalate. Compounds **16c**, **22a—d**, **37** and **52** were prepared by this method.

b) To a stirred suspension of $LiAlH_4$ (0.6 g) in tetrahydrofuran (THF) (30 ml) was added dropwise a solution of **15a** (1.2 g) in THF (20 ml). After the mixture was refluxed for 4 hr, to the reaction mixture was added dropwise water (5 ml). The mixture was filtered, and the filtrate was extracted with AcOEt (200 ml). The extract was washed water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was converted to oxalate by the addition of saturated ethereal solution of oxalic acid and recrystallized from MeOH–ether to give **16a** (1.0 g) as colorless needles. Compound **16b** was prepared from **15b** by the same procedure.

c) To a stirred suspension of $LiAlH_4$ (1.0 g) in THF (50 ml) was added **22a** (1.5 g) and the mixture was refluxed for 3 hr. After AcOEt (10 ml) and saturated aq. $NaHCO_3$ (10 ml) were added dropwise to the mixture, the mixture was filtered. The filtrate was extracted with AcOEt (200 ml). The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in ethanolic HCl (20 ml), treated with activated charcoal diluted with ether (50 ml), and allowed to stand at room temperature. The resulting crystals were collected by filtration to give **23** (0.7 g) as colorless needles, mp 220—222°.

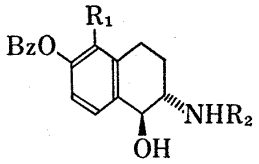
d) A solution of *trans*-6-benzyloxy-2-isopropylamino-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**24**)[6] (20 g) in EtOH (300 ml) was refluxed with stirring, while to the solution was added Raney Ni (5.0 g) and then dropwise a solution of NH_2NH_2·H_2O (20 g) in EtOH (40 ml) over a period of 1 hr. After the mixture was refluxed for further 30 min, the Raney Ni was removed by filtration and evaporated *in vacuo*. The residue was triturated with ether to give **25** (7.0 g) as colorless needles.

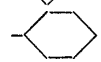
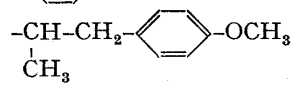
e) To a stirred solution of **25** (2.0 g) in AcOH (80 ml) was added portionwise $NaBH_4$ (8 g). After stirring for 7 hr at room temperature, the mixture was poured into water (200 ml), made alkaline with $NaHCO_3$ and extracted with AcOEt (600 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from ether to give **26** (1.1 g) as colorless needles.

f) To a stirred solution of **25** (2.0 g) in AcOH (80 ml) was added portionwise $NaBH_4$ (8.0 g) and the mixture was stirred for 5 days at room temperature. The mixture was poured into water (400 ml), made alkaline with $NaHCO_3$ and extracted with AcOEt (500 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from ether to give **27** (0.9 g) as colorless needles.

g) To a solution of **25** (0.6 g) in MeOH (6 ml) and AcOH (1 ml) was added a solution of KCNO (0.6 g) in water (3 ml) with vigorous stirring. After the addition was completed, stirring was continued for 1 hr

TABLE V. N,N′-Substituted 2,5-Diamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol



Compound No.	R_1	R_2	Salt	Yield (%)	mp (°C)	NMR-Spectrum C_1–H ppm	NMR-Spectrum $J_{1,2}$ Hz	Formula	Analysis (%) Calcd. (Found) C	H	N
16a	$N(CH_3)Bz$	CH_3	Oxalate	77	191—192	4.74[a]	8	$C_{26}H_{30}N_2O_2 \cdot C_2H_2O_4$	68.27 (68.05)	6.55 (6.41)	5.69 (5.52)
16b	$N(CH_3)Bz$	C_2H_5	Oxalate	68	178—180	4.80[a]	8	$C_{27}H_{32}N_2O_2 \cdot C_2H_2O_4$	68.75 (68.70)	6.77 (6.54)	5.53 (5.38)
16c	$N(CH_3)Bz$	$CH(CH_3)_2$	Oxalate	70	193—195	4.90[a]	9	$C_{28}H_{34}N_2O_2 \cdot C_2H_2O_4$	69.21 (69.44)	6.97 (6.96)	5.38 (5.30)
22a	$N(CH_3)COOBz$	$CH(CH_3)_2$	HCl	73	224—226	4.70[a]	9	$C_{29}H_{34}N_2O_4 \cdot HCl$	70.11 (70.05)	6.90 (6.73)	5.48 (5.21)
22b	$N(CH_3)COOBz$		Oxalate	65	119—121	4.80[a]	9	$C_{30}H_{34}N_2O_4 \cdot C_2H_2O_4$	66.65 (66.40)	6.29 (6.18)	4.86 (4.70)
22c	$N(CH_3)COOBz$		HCl	85	152—153	4.90[a]	8	$C_{32}H_{38}N_2O_4 \cdot HCl$	69.74 (69.71)	7.13 (7.10)	5.08 (5.10)
22d	$N(CH_3)COOBz$		HCl	67	143—145	5.00[a]	9	$C_{36}H_{40}N_2O_5 \cdot HCl$	70.17 (69.92)	6.54 (6.49)	4.55 (4.50)
23	$N(CH_3)_2$	$CH(CH_3)_2$	HCl	67	220—222	5.00[a]	8	$C_{22}H_{30}N_2O_2 \cdot 2HCl$	61.82 (61.66)	7.55 (7.38)	6.56 (6.61)
25	NH_2	$CH(CH_3)_2$		42	218—220	4.50[b]	8	$C_{20}H_{26}N_2O_2$	73.56 (73.28)	8.03 (8.00)	8.58 (8.78)
26	NHC_2H_5	$CH(CH_3)_2$		63	120—122	4.34[b]	8	$C_{22}H_{30}N_2O_2$	74.54 (74.66)	48.53 (8.31)	7.90 (7.74)
27	$N(C_2H_5)_2$	$CH(CH_3)_2$		71	126—128	4.60[b]	8	$C_{24}H_{34}N_2O_2$	75.35 (75.41)	8.96 (8.77)	7.32 (7.30)
37	$N(SO_2CH_3)Bz$	$CH(CH_3)_2$	HCl	45	212—214	4.95[a]	9	$C_{28}H_{34}N_2O_4S \cdot HCl$	60.18 (60.29)	6.31 (6.46)	5.02 (5.20)
38	$NHCONH_2$	$CH(CH_3)_2$		74	oil	4.50[b]	8	$C_{21}H_{27}N_3O_3$	—	—	—
52	Cl	$CH(CH_3)_2$	HCl	53	265—267	5.00[a]	8	$C_{20}H_{24}ClNO_2 \cdot HCl$	60.00 (59.96)	6.80 (6.83)	3.50 (3.42)

a) In d_6-DMSO. *b*) In $CDCl_3$. Bz: $CH_2C_6H_5$.

and the mixture was evaporated *in vacuo*. The residue was poured into water (100 ml), made alkaline with $NaHCO_3$ and then extracted with AcOEt (200 ml). The extract was washed with water, treated with activated charcoal and evaporated *in vacuo* to give **38** (0.5 g) as a colorless oil. IR ν_{max}^{Neat} cm^{-1}: 1685 (C=O). MS *m/e*: 369 (M^+), 351 ($M-H_2O$).

***trans*-5-Amino-2-benzylmethylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (42)**——A solution of *trans*-2-benzylmethylamino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**40**)[6] (4.0 g) in EtOH (40 ml) was refluxed with stirring, while to this solution was added Raney Ni (1.3 g) and then dropwise a solution of $NH_2NH_2 \cdot H_2O$(4.0 g) in EtOH (40 ml) over a period of 30 min. After refluxing for further 30 min, the catalyst was filtered and the filtrate was concentrated to 20 ml *in vacuo*. The resulting precipitate was collected by filtration and recrystallized from MeOH to give **42** (2.0 g, 59%) as colorless prisms, mp 124—126°. *Anal.* Calcd. $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 77.11; H, 7.00; N, 7.09. NMR (in $CDCl_3$) δ: 2.24 (3H, s, N–CH_3), 4.62 (1H, d, J=9 Hz, C_1–H).

***cis*-5-Amino-2-benzylmethylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenol (41)**——Similar procedures as mentioned above using *cis*-2-benzylmethylamino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**39**)[6] (3.0 g), Raney Ni (1.0 g) and $NH_2NH_2 \cdot H_2O$ (3.0 g) afforded **41** (1.8 g, 70%) as colorless prisms, mp 148—150°. *Anal.* Calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21. Found: C, 77.14; H, 7.35; N, 7.21. NMR (in d_6-DMSO) δ: 2.60 (3H, s, N–CH_3), 4.94 (1H, d, J=2 Hz, C_1–H).

***trans*-2-Benzylmethylamino-6-benzyloxy-5-ureido-1,2,3,4-tetrahydro-1-naphthalenol (44)**——To a solution of **42** (0.5 g) in a mixture of MeOH (5 ml) and AcOH (1 ml) was added dropwise a solution of KCNO (0.5 g) in water (3 ml) with vigorous stirring at room temperature. After the addition was completed, stirring was continued for further 1 hr and the mixture was evaporated *in vacuo*. The residue was poured into water (50 ml), made alkaline with $NaHCO_3$ and extracted with AcOEt (100 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give **44** (0.5 g, 90%) as a colorless viscous oil. IR ν_{max}^{Neat} cm^{-1}: 1690 (C=O). MS *m/e*: 431 (M^+), 413 ($M-H_2O$).

***cis*-2-Benzylmethylamino-6-benzyloxy-5-ureido-1,2,3,4-tetrahydro-1-naphthalenol (43)**——The same procedures as above using **41** afforded **43** (0.5 g, 90%) as a colorless viscous oil. IR ν_{max}^{Neat} cm^{-1}: 1685 (C=O). MS *m/e*: 431 (M^+).

***trans*-2-Benzylmethylamino-6-benzyloxy-5-formamido-1,2,3,4-tetrahydro-1-naphthalenol (46)**——A mixture of **42** (1.0 g), HCOOH (3 ml) and Ac_2O (5 ml) was allowed to stand overnight at room temperature. After evaporation of the mixture *in vacuo*, to the residue was added MeOH (50 ml) and a solution of Na_2CO (2.0 g) in water (2 ml), and the mixture was stirred for 1 hr. The mixture was evaporated again *in vacuo* and the residue was extracted with AcOEt (200 ml). Evaporation of the extract followed by column chromatography on silica gel (acetone–benzene=1 : 1) gave **46** (0.3 g, 28%) as a colorless viscous oil. MS *m/e*: 416 (M^+), 398 ($M-H_2O$). IR ν_{max}^{Neat} cm^{-1}: 1690 (C=O).

***cis*-2-Benzylmethylamino-6-benzyloxy-5-formamido-1,2,3,4-tetrahydro-1-naphthalenol (45)**——The same procedure as above using **41** afforded **45** (0.4 g, 37%) as pale brown needles, mp 124—125°. *Anal.* Calcd. for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 74.64; H, 6.56; N, 6.99. NMR (in $CDCl_3$) δ: 4.90 (1H, d, J=2 Hz, C_1–H).

N,N′-Substituted 2,5-Diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (2a—q) (Table I)——General Procedure: N,N′-Disubstituted 2,5-diamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenols (**16**, **21**—**23**, **26**, **27**, **36**—**38** and **43**—**46**) (3 mmol) was subjected to catalytic hydrogenation in MeOH (30 ml) over 10% Pd-C (1.0 g) under an atmospheric pressure at room temperature until the absorption of H_2 ceased. After removal of the catalyst by filtration, to the filtrate was added 20% ethanolic HCl (5 ml) or saturated ethereal solution of fumaric acid (10 ml). The solution was then diluted with ether until it became a little turbid. On standing the solution, the objective compound (**2a**—**q**) deposited as crystals of the hydrochloride or the fumarate. Thus, by these procedures **2a** was prepared from **21**, **2b** from **16a**, **2c** from **16b**, **2d**—**g** from the corresponding **22**, **2h** from **23**, **2i** from **26**, **2j** from **27**, **2k** from **36**, **21** from **37**, **2m** from **43**, **2n** from **44**, **2o** from **38**, **2p** from **45**, and **2q** from **46**. The yields, mp and elemental analyses of the compounds are listed in Table I.

***trans*-5-Chloro-6-hydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (53)**——A solution of **52** (0.2 g) in EtOH (10 ml) was hydrogenated over 5% Pd-C (0.2 g) under an atmospheric pressure until stoichiometric amount of H_2 was absorbed. After removal of the catalyst, the filtrate was diluted with ether (20 ml) to precipitate **53**·HCl (0.1 g, 66%) as colorless needles, mp 204° (dec.). *Anal.* Calcd. for $C_{13}H_{18}ClNO \cdot HCl$: C, 53.43; H, 6.55; N, 4.79. Found: C, 53.50; H, 6.48; N, 4.49. NMR (in d_6-DMSO) δ: 1.32 (3H, d, J=6 Hz, CH_3), 1.46 (3H, d, J=6 Hz, CH_3), 4.80 (1H, d, J=8 Hz, C_1–H).

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