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

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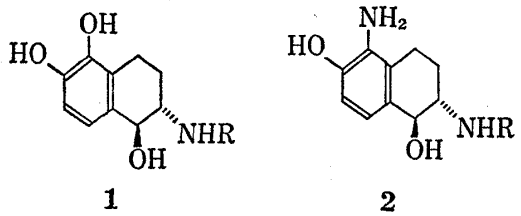
A series of 2-substituted amino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**2**) was synthesized starting with 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**3**). Thus, 6-hydroxy–tetralone (**4**), prepared by demethylation of **3**, was nitrated to give a mixture of 5-nitro (**5**) and 7-nitro (**6**) derivatives. Compound **5** was led to the oxime tosylate (**9**) *via* compounds **7**, **8**. Neber rearrangement of **9** into α-amino ketone (**10**) followed by reduction with sodium borohydride afforded *trans*-2-amino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**11**), from which compounds **2a**, **2b** and **2d—r** were derived. The 2-methylamino derivative (**2c**) was prepared *via* two alternative routes. Most of the compounds **2** exhibited potent β-adrenoceptor agonistic activity with considerable β_2-selectivity. However, compound **24**, a position isomer of **2d** which was prepared from **6** by the similar procedures, showed no β-adrenoceptor activity.

Keywords——tetrahydronaphthalenol; catecholamine derivative; tetrahydronaphthylamine; rigid catecholamine; β_2-adrenoceptor agonist; β_2-selectivity

In previous papers we reported the syntheses and potent β_2-adrenoceptor agonist activities of N-substituted 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**), which are conformationally rigid derivatives of adrenergic catecholamines.[2–4] Excellent biological activities exhibited by the *trans* isomers of **1** suggested that functional moieties in these compounds, *i.e.* the amino ethanol moiety and hydroxyl groups, are arranged so as to occupy favorable positions for the interaction with the active site of the β-adrenoceptor. On the other hand, the recent extensive studies on the structure–activity relationships for β-adrenoceptor agonists have demonstrated that the replacement of the *meta*-phenolic hydroxyl group in catecholamines with a variety of other functional groups has often resulted in improved selectivity for β_2-adrenoceptor and increased duration of action owing to the inhibition of inactivation by O-methyltransferase (COMT). Among the successful examples of the *meta*-substituent are hydroxymethyl (Sulbutamol),[5] methanesulfonylamino (Soterenol)[6] and ureido (Carbuterol)[7] groups. In view of these results, our attention has been directed to the modifications of **1** by replacing the 5-hydroxyl group with other functional groups.



1 **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) D.T. Collin, D. Hartley, D. Jack, L.H.C. Lunts, J.C. Press, A.C. Ritchie, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).
6) R.H. Uloth, J.R. Kirk, W.A. Gould, and A.A. Larsen, *J. Med. Chem.*, **10**, 462 (1967).
7) C. Kaiser, D.F. Colella, M.S. Schartz, E. Garvey, and J.R. Wardell, Jr., *J. Med. Chem.*, **17**, 49 (1974).

The present paper deals with the syntheses of *trans*-2-substituted amino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol derivatives (**2**), the 5-amino analogues of **1**, as the continuation of the previously reported modification by introducing a variety of carbon substituents at the 5-position.[8]

As the starting material for the syntheses of **2** was employed commercially available 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**3**). Treatment of **3** with hydrobromic acid or aluminum chloride gave the 6-hydroxy derivative (**4**), which was nitrated with nitric acid in sulfuric acid to give a mixture of 5-nitro (**5**) and 7-nitro (**6**) compounds. Each isomer was readily separated by fractional recrystallization from benzene, affording **5** and **6** in 42% and 17% yields, respectively. Compound **5** was led to 6-benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone oxime O-*p*-toluenesulfonate (**9**) by the three steps of reactions; benzylation to **7**, treatment with hydroxylamine to give an oxime (**8**), and the reaction with *p*-toluenesulfonyl chloride. Neber rearrangement of **9** with potassium ethoxide afforded 2-amino-6-benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**10**) in 83% yield. This rearrangement also proceeded with sodium ethoxide in a somewhat lower yield of 71%. Reduction of **10** with sodium borohydride ($NaBH_4$) resulted in the selective formation of *trans*-amino alcohol (**11**). The 1,2-*trans* conformation of **11** was determined on the basis of the nuclear magnetic resonance (NMR) spectrum, in which the proton at the 1-position was observed as a doublet at δ 4.60 with a coupling constant ($J_{1,2}$) of 10 Hz.[2-4] Compound **11** was allowed to react

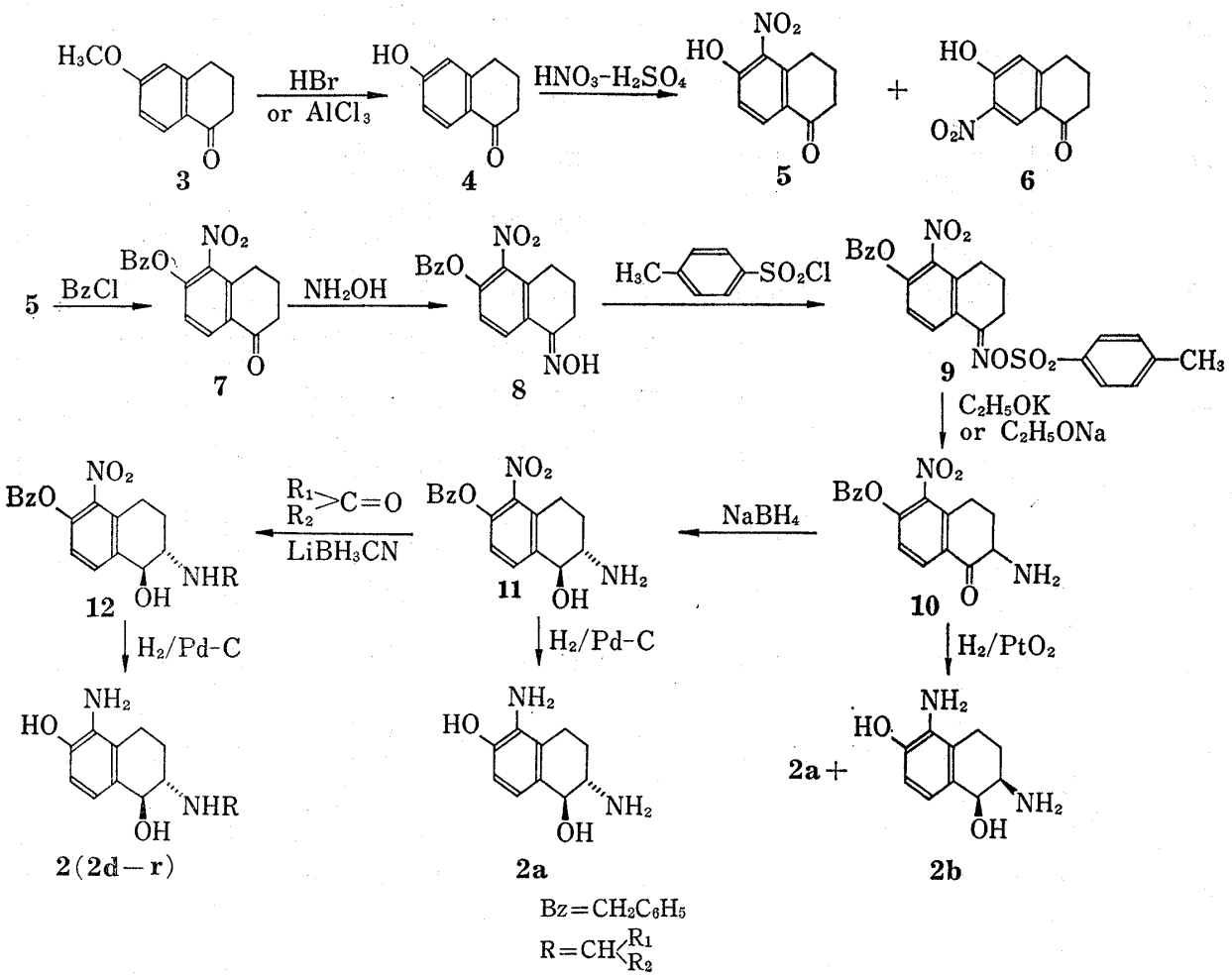
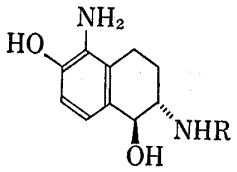


Chart 2

8) H. Sugihara, K. Ukawa, H. Kuriki, M. Nishikawa, and Y. Sanno, *Chem. Pharm. Bull.* (Tokyo), **25**, 2988 (1977).

with a wide variety of ketones and aldehydes in the presence of lithium cyanoborohydride ($LiBH_3CN$) or sodium cyanoborohydride ($NaBH_3CN$)[9] to give N-substituted 2-amino derivatives (**12**) (Table III).

TABLE I. *trans*-2-Substituted Amino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**2**)



Compound No.	R	Salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	H	HCl	75	>300	$C_{10}H_{14}N_2O_2 \cdot 2HCl$	44.95 (44.57)	6.04 (6.20)	10.49 (10.22)
2c	CH_3	Fumarate	82	>300	$C_{11}H_{16}N_2O_2 \cdot C_4H_4O_4$	55.55 (55.30)	6.22 (6.18)	8.64 (8.47)
2d	$-CH(CH_3)$	HCl	94	212—214	$C_{13}H_{20}N_2O_2 \cdot 2HCl$	50.49 (50.44)	7.17 (6.95)	9.06 (9.20)
2e	$-CH(CH_3)CH_2CH_3$	HCl	62	215—216	$C_{14}H_{22}N_2O_2 \cdot 2HCl \cdot 2H_2O$	46.90 (47.13)	7.85 (7.47)	7.80 (7.53)
2f	$-CH(CH_3)-CH(CH_3)$	HCl	66	220—222	$C_{15}H_{24}N_2O_2 \cdot 2HCl \cdot 2H_2O$	48.52 (48.52)	7.55 (7.16)	7.54 (7.33)
2g	$-CH(CH_3)-CH_2-CH(CH_3)$	HCl	68	222—223	$C_{16}H_{26}N_2O_2 \cdot 2HCl \cdot 2H_2O$	49.61 (50.01)	8.32 (8.07)	7.23 (7.22)
2h	$-CH_2CH_2OCH_3$	Fumarate	45	162—164	$C_{13}H_{20}N_2O_3 \cdot C_4H_4O_4$	55.45 (55.41)	6.56 (6.87)	7.61 (7.46)
2i	$-CH_2-C_6H_5$	HCl	54	230—234	$C_{17}H_{26}N_2O_2 \cdot 2HCl$	56.20 (55.82)	7.77 (7.49)	7.71 (7.85)
2j	$-C_6H_5$	HCl	75	205—207	$C_{14}H_{20}N_2O_2 \cdot 2HCl \cdot 3/2H_2O$	48.27 (48.63)	7.24 (7.76)	8.05 (8.06)
2k	$-C_6H_5$	HCl	71	206—209	$C_{16}H_{24}N_2O_2 \cdot 2HCl \cdot 3/2H_2O$	51.12 (50.80)	7.79 (8.03)	7.02 (7.07)
2l	$-C_6H_4-CH_3$	HCl	77	218—220	$C_{19}H_{26}N_2O_2 \cdot 2HCl \cdot 2H_2O$	51.06 (51.12)	7.78 (8.08)	7.45 (7.12)
2m	$-C_6H_4-N(CH_3)$	HCl	55	212—214	$C_{16}H_{25}N_3O_2 \cdot 3HCl \cdot 2H_2O$	43.99 (43.47)	7.38 (7.23)	9.62 (9.55)
2n	$-CH(CH_3)CH_2-C_6H_5$	HCl	75	Amorphous	$C_{19}H_{24}N_2O_2 \cdot 2HCl$	56.86 (57.23)	6.53 (6.10)	6.98 (7.09)
2o	$-CH(CH_3)CH_2-C_6H_4-OCH_3$	HCl	40	240—242	$C_{20}H_{26}N_2O_3 \cdot 2HCl \cdot 2H_2O$	53.21 (52.82)	7.15 (7.06)	6.20 (6.38)
2p	$-CH(CH_3)CH_2-C_6H_4-OH$	HCl	63	198—203	$C_{19}H_{24}N_2O_3 \cdot 2HCl \cdot 3/2H_2O$	53.27 (53.44)	6.82 (6.59)	6.54 (6.28)
2q	$-CH(CH_3)-CH_2-C_8H_6N$	Fumarate	53	>300	$C_{21}H_{25}N_3O_2 \cdot C_4H_4O_4$	64.22 (63.84)	6.25 (6.16)	8.99 (9.13)
2r	$-CH_2-C_4H_7O$	Fumarate	41	185—188	$C_{16}H_{24}N_2O_3 \cdot C_4H_4O_4$	58.81 (58.59)	6.91 (6.90)	6.85 (7.03)

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

Catalytic reduction of **11** over palladium-charcoal effected debenzylation and reduction of the nitro group to afford *trans*-2,5-diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**2a**). Although it was expected that **2a** would also be obtained directly from **10** by simultaneous reduction of the 1-carbonyl, 6-benzyloxy and 5-nitro groups, catalytic reduction of **10** over platinum oxide in the presence of a small amount of water was found to afford *ca.* 1: 2 mixture of *trans* (**2a**) and *cis* (**2b**) compounds from the observation of the NMR spectrum, which showed the signal for proton at the 1-position as two overlapped doublets ($J_{1,2}$=8 Hz and 3 Hz). Compounds **12** were catalytically hydrogenated over palladium-charcoal to afford a variety of desired 2-alkylamino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**2d—r**), which are listed in Table I. The compound **2r** was prepared from N-(3,4-dihydro-2*H*-pyran-1-yl)methyl derivative (**12o**) by reducing the double bond of the dihydropyranyl group simultaneously with the nitro and the benzyloxy groups.

The 2-methylamino derivative (**12**: R=CH_3) was not obtained by a similar reductive methylation of **11** with formaldehyde owing to the formation of the 2-dimethylamino derivative. Accordingly, the preparation of **2c** was carried out *via* the following alternative route. Compound **10** was converted to 2-benzylamino ketone (**13**) by the reaction with benzaldehyde and $NaBH_3CN$. The reaction of **13** with $NaBH_4$ gave a mixture of *trans*- and *cis*-2-benzylamino alcohol (**14**) in contrast to the case of **10**, in which the *trans* compound was predominanly afforded. The isomeric mixture of **14** was allowed to react with formaldehyde in formic acid to give a mixture of *trans*- and *cis*-2-benzylmethylamino derivatives (**15a, b**), which were separated to each other by column chromatography to give 49% and 29% yields, respectively. Catalytic hydrogenation of **15a** gave rise to **2c** by the simultaneous removal of the two benzyl groups and the reduction of the nitro group. The compounds **15a, 15b** were also derived from bromo ketone derivative (**16**), which was obtained by bromination of **7** with pyridine hydroperbromide, by substitution with methylbenzylamine, reduction with $NaBH_4$ and separation of each isomer with column chromatography in the yields of 16% and 9%, respectively.

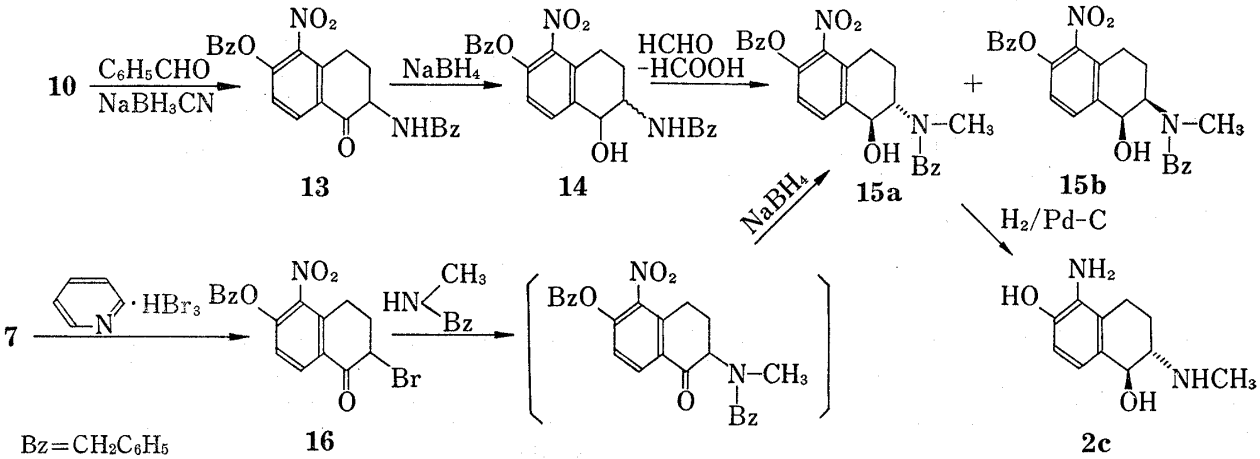


Chart 3

TABLE II. β-Adrenoceptor Activity of *trans*-2-Substituted Amino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols

Compound No.	Isolated atria (β_1)			Isolated tracheal strip (β_2)			Separation ratio[d]
	n[a]	PD_2[b]	*i.a.*[c]	n[a]	PD_2[b]	*i.a.*[c]	
2d	4	6.58±0.18	0.9	8	7.74±0.14	1.0	15.2
2j	4	8.46±0.35	0.9	4	8.88±0.17	1.0	2.63
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.

The β_1- and β_2-adrenoceptor activities of some of the compounds **2** were measured *in vitro* using, respectively, isolated atrial preparations and tracheal strips of guinea pig according to the methods described in a foregoing paper.[2] In a preliminary test, most of the compounds exhibited potent activity for the tracheal preparation with pD_2 ranging from 7 to 9 and showed considerable β_2-selectivity superior to that of *l*-isoproterenol. Table II shows the data for two compounds, **2d** and **2j**, which have been examined in some detail.

In view of the above biological results, it became of interest to investigate the activity of 7-amino-6-hydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (**24**), a position isomer of **2d**. Accordingly, compound **6** obtained as a by-product during the above-mentioned nitration of **4** was led to 2-amino-6-benzyloxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**20**) by a sequence of similar transformations, *i.e.* O-benzylation, oxime formation, O-tosylation of the oxime, and Neber rearrangement by way of compounds **17**, **18** and **19**. Reduction of **20** with $NaBH_4$ effected selective formation of *trans*-amino alcohol (**21**), which was catalytically reduced to give 2,7-diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**23**). Reductive N-isopropylation of **21** to give **22** followed by catalytic hydrogenation yielded **24**.

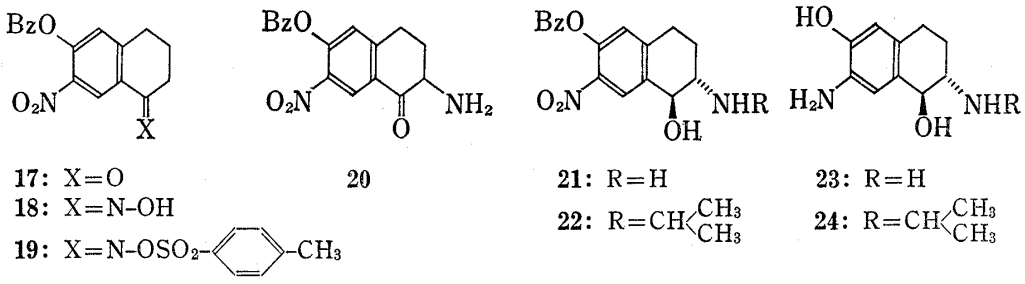


Chart 4

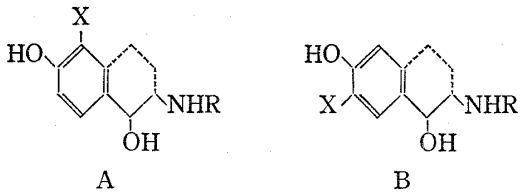


Chart 5

It was found, however, that **24** showed virtually no β-adrenoceptor activity. This result suggests that the actual configurations of *m*-modified catecholamine analogues might be depicted as A in Chart 5 rather than B as in the case of prototype catecholamines discussed in the preceding paper.[2]

Experimental[10]

6-Hydroxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (5) and 6-Hydroxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (6)——To a stirred solution of 6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone[11] (**4**) (15 g) in H_2SO_4 (60 ml) was added dropwise a mixture of H_2SO_4 (12 ml) and HNO_3 (d=1.38) (8 ml) at 0° over a period of 0.5 hr. After addition was completed, the mixture was stirred for further 10 min, poured into ice-water (1000 ml) and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was suspended in hot benzene and the insoluble substance was collected by filtration to give crude **5**, which was recrystallized from EtOH to give **5** (8.0 g, 42%) as pale yellow prisms, mp 196—198°. *Anal.* Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.10; H, 4.26; N, 6.70. IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). NMR (in $CDCl_3$) δ: 7.10 (1H, d, J=8 Hz, aromatic-H), 8.00 (1H, d, J=8 Hz, aromatic-H).

The filtrate was decolorized with active charcoal and evaporated *in vacuo*. Recrystallization of the residue from EtOH gave **6** (3.7 g, 19%) as yellow leaflets, mp 139—140°. *Anal.* Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.87; N, 4.13; N, 6.74. IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O). NMR (in $CDCl_3$) δ: 7.00 (1H, s, aromatic-H), 9.02 (1H, s, aromatic-H).

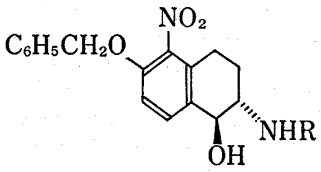
10) All melting points were taken on a Kofler-type hot-stage apparatus (Yanagimoto Co.) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on Varian HA-100 or A-60 high resolution spectrometers.

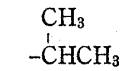
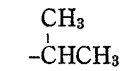
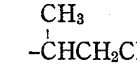
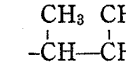
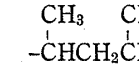
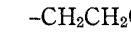
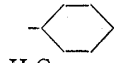
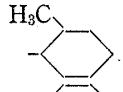
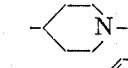
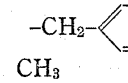
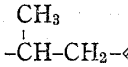
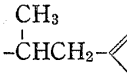
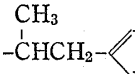
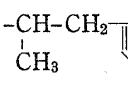
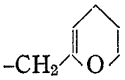
11) J.A. Durden, Jr., *J. Agr. Food Chem.*, **19**, 432 (1971).

6-Benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (7)——A mixture of **5** (14 g), benzyl chloride (8.8 g), anhydrous K_2CO_3 (4.9 g), KI (1.0 g) and dimethylformamide (DMF) (140 ml) was heated with stirring at 80° for 3 hr. The cooled mixture was poured into ice-water (1000 ml). The resulting precipitate was collected by filtration and recrystallized from EtOH to give **7** (18 g, 90%) as colorless prisms, mp 105—107°. *Anal.* Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.60; H, 4.96; N, 4.45.

6-Benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone Oxime (8)——A mixture of **7** (6.0 g), anhydrous K_2CO_3 (5.5 g) and $NH_2OH \cdot HCl$ (5.5 g) in MeOH (160 ml) and water (16 ml) was heated with stirring for 2 hr.

TABLE III. *trans*-2-Substituted Amino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**12**)



Compound No.	R	Method	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
12a		A	76	271	$C_{20}H_{24}N_2O_4 \cdot HCl$	61.14 (61.31)	7.13 (7.25)	6.41 (6.58)
12a		C	64	271	—	— (—)	— (—)	— (—)
12b		A	87	250—252	$C_{21}H_{26}N_2O_4 \cdot HCl$	61.98 (61.73)	6.69 (6.48)	6.89 (6.60)
12c		A	80	250—253	$C_{22}H_{28}N_2O_4 \cdot HCl$	62.77 (62.56)	6.94 (6.67)	6.66 (6.51)
12d		A	85	225—227	$C_{23}H_{30}N_2O_4 \cdot HCl$	63.51 (63.68)	7.19 (7.30)	6.44 (6.50)
12e		B	71	195—197	$C_{20}H_{24}N_2O_5 \cdot HCl \cdot EtOH$	58.07 (58.32)	6.87 (6.69)	6.16 (5.85)
12f		A	70	242—244	$C_{21}H_{24}N_2O_4 \cdot HCl$	62.29 (62.10)	6.22 (6.34)	6.92 (6.75)
12g		A	83	271—273	$C_{23}H_{28}N_2O_3 \cdot HCl \cdot H_2O$	61.39 (61.01)	6.72 (6.42)	6.23 (6.17)
12h		A	88	218—220	$C_{24}H_{30}N_2O_4 \cdot HCl$	64.49 (64.15)	6.99 (6.70)	6.27 (6.09)
12i		A	77	212—214	$C_{23}H_{29}N_3O_4 \cdot 2HCl$	57.02 (57.15)	6.45 (6.41)	8.67 (8.53)
12j		B	84	241—242	$C_{24}H_{24}N_2O_4 \cdot HCl$	65.37 (65.40)	5.72 (5.52)	6.35 (6.30)
12k		B	70	204—206	$C_{26}H_{28}N_2O_4 \cdot HCl$	66.58 (66.50)	6.23 (6.04)	5.98 (5.59)
12l		B	65	228—230	$C_{27}H_{30}N_2O_5 \cdot HCl$	64.98 (64.95)	6.26 (5.86)	5.62 (5.86)
12m		B	65	232—235	$C_{26}H_{28}N_2O_5 \cdot HCl$	64.39 (64.09)	6.02 (6.21)	5.78 (5.53)
12n		A	57	215—217	$C_{28}H_{29}N_3O_4 \cdot HCl$	66.20 (65.99)	5.95 (5.81)	8.27 (8.13)
12o		B	35	175—178	$C_{23}H_{26}N_2O_5$	67.30 (67.36)	6.39 (6.31)	6.83 (6.51)

The reaction mixture was poured into ice-water (500 ml) and the resulting precipitate was recrystallized from MeOH to give **8** (6.5 g, 93%) as colorless needles, mp 178—180°. *Anal.* Calcd. for $C_{17}H_{16}NO_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.40; H, 5.07; N, 8.67.

6-Benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-*p*-Toluenesulfonate (9)——To a solution of **8** (26 g) in pyridine (100 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (33 g) in pyridine (50 ml). After stirring at room temperature for 5 hr, the mixture was poured into ice-water (1000 ml). The resulting precipitate was filtered, washed with water, and recrystallized from benzene to give **9** (34.8 g, 88%) as colorless needles, mp 152—153°. *Anal.* Calcd. for $C_{24}H_{22}N_2O_6S$: C, 61.79; H, 4.75; N, 6.01. Found: C, 61.97; H, 4.61; N, 5.99.

2-Amino-6-benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (10)——a) To a stirred solution of **9** (24 g) in dry benzene (300 ml) was added dropwise a cooled solution of EtOK, prepared from K (2.2 g) and abs. EtOH (60 ml), under nitrogen at 5°. After addition was completed, the reaction mixture was allowed to stand overnight in a refrigerator. The precipitate deposited in the dark green mixture was removed by filtration and washed with dry ether. To the combined solution of the filtrate and the washings was added conc. HCl (20 ml) with stirring at room temperature. The resulting precipitate was collected by filtration and dissolved in hot MeOH (300 ml). After treatment with active charcoal, the solution was diluted with ether (500 ml). The resulting precipitate was collected by filtration to give **10**·HCl (14.4 g, 83%) as colorless leaflets, mp 220—223°. *Anal.* Calcd. for $C_{17}H_{16}N_2O_4$·HCl: C, 58.54; H, 4.91; N, 8.03. Found: C, 58.60; H, 5.16; N, 7.64. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O).

b) To a stirred solution of **9** (140 g) in dry benzene (2000 ml) was added dropwise at 5° a cooled solution of EtONa, prepared from Na (7.6 g) and abs. EtOH (330 ml). After addition was completed, the reaction mixture was stirred at 5° for 24 hr. The precipitate deposited in the dark green reaction mixture was filtered and washed with dry ether. To the combined solution of the filtrate and the washings was added conc. HCl (100 ml) with stirring at room temperature. The filtration of the resulting precipitate followed by the similar treatment to the case of a) afforded **10**·HCl (74 g, 71%).

***trans*-2-Amino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (11)**——To a stirred solution of **10**·HCl (17 g) in MeOH (170 ml) was added portionwise $NaBH_4$ (4.4 g). After being stirred for further 0.5 hr, the solution was poured into ice-water (500 ml) and extracted with AcOEt (300 ml). The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in MeOH (100 ml) and to the solution was added 20% HCl–EtOH (10 ml). Upon addition of ether (200 ml) to the mixture, **11**·HCl (13.6 g, 80%) deposited as colorless needles, mp 213—215°. *Anal.* Calcd. for $C_{17}H_{18}N_2O_4$: C, 58.20; H, 5.46; N, 7.99. Found: C, 58.34; H, 5.59; N, 7.68. NMR (in d_6-DMSO) δ: 4.60 (1H, d, J=10 Hz, C_1–H).

***trans*-2-Substituted Amino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol Derivatives (12) (Table III)**——General procedure. a) Method A: To an ice-cooled mixture of **11**·HCl (1.0 g) and a ketone or an aldehyde (3—5 g) in MeOH (30 ml) was added portionwise $LiBH_3CN$·2 dioxane (1.0 g) with stirring. After being stirred for 5—12 hr, the solution was poured into water (100 ml), made slightly acidic with 10% HCl, then neutralized with $NaHCO_3$, and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 20% HCl–EtOH (10 ml) and diluted with ether (10 ml), whereupon **12** precipitated as crystals of the hydrochloride.

b) Method B: To a stirred mixture of **11**·HCl (1.0 g) and a ketone or an aldehyde (3—5 g) in MeOH (30 ml) was added, in portions, $NaBH_3CN$ (0.5 g) at room temperature. After stirring for 5 hr, the mixture was poured into water (100 ml), made slightly acidic with 10% HCl, neutralized with $NaHCO_3$ and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. Treatment of the residue in a similar manner to a) afforded **12**·HCl.

c) Method C: Compound **11**·HCl (70 g) was neutralized with $NaHCO_3$ in water (1000 ml) and extracted with AcOEt (500 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting free base of **11** was dissolved in a mixture of benzene (350 ml) and acetone (350 ml) and the solution was refluxed with stirring for 2 hr. After evaporation of the solution, the residue was dissolved in MeOH (500 ml). To the solution was added portionwise $NaBH_4$ (10 g) with stirring under ice-cooling. After 30 min, the mixture was poured into ice-water (2000 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% HCl–EtOH (200 ml) and then diluted with ether (200 ml), whereupon **12a**·HCl (51 g, 64%) precipitated as colorless needles.

2-Benzylamino-6-benzyloxy-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (13)——To a stirred solution of **10** (6.9 g) in MeOH (130 ml) was added benzaldehyde (6.1 g) and $NaBH_3CN$ (1.5 g) at room temperature. After stirring for 5 hr, the mixture was allowed to stand overnight at room temperature. The resulting precipitate was collected by filtration and dissolved in 20% HCl–EtOH (50 ml). The solution was diluted with ether (100 ml) to precipitate **13** (5.4 g, 70%) as pale yellow prisms, mp 173—176°. *Anal.* Calcd. for $C_{24}H_{22}N_2O_4$·HCl: C, 65.67; H, 5.28; N, 6.38. Found: C, 65.63; H, 5.18; N, 6.30. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O).

6-Benzyloxy-2-bromo-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (16)——To a stirred solution of **7** (6.0 g) in AcOH (60 ml) was added pyridine hydrobromide perbromide (C_6H_5N·HBr_3) (7.0 g) at room temperature. After stirring for 1 hr, the mixture was poured into ice-water (500 ml). The resulting precipitate was collected

by filtration and purified by column chromatography on silica gel (eluant: benzene) to give **16** (6.0 g, 79%) as colorless needles, mp 95—97°. *Anal.* Calcd. for $C_{17}H_{14}NO_4Br$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.56; H, 3.44; N, 3.58. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O).

***trans*- and *cis*-2-(N-Benzyl-N-methylamino)-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (15a and 15b)**——a) To a stirred solution of **13** (12 g) in MeOH (100 ml) was added in portions $NaBH_4$ (3.5 g) at room temperature. After stirring for 30 min, the mixture was poured into ice-water (500 ml). The resulting precipitate was collected by filtration to give 2-benzylamino-6-benzyloxy-5-nitro-1,2,3,4-tetrahydro-1-naphthalenol (**14**) as colorless needles (10 g, 90%), which were submitted to the subsequent procedure without further purification. A mixture of **14** (10 g), formic acid (100 ml) and formalin (100 ml) was refluxed for 5 hr. After evaporation of the reaction mixture *in vacuo*, to the residue was added water (200 ml). The solution was made alkaline with NH_4OH and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was submitted to column chromatography on silica gel and eluted with acetone–benzene (1: 9). The first fraction was evaporated to give **15a** as a colorless oil, which was converted to the hydrochloride to give **15a**·HCl (5.5 g, 49%) as colorless needles, mp 251—253°. *Anal.* Calcd. for $C_{25}H_{26}N_2O_4$·HCl: C, 66.00; H, 5.98; N, 6.16. Found: C, 66.31; H, 5.73; N, 6.21. NMR (in d_6-DMSO) δ: 5.00 (1H, d, J=7 Hz, C_1–H).

Further elution with the same solvent gave **15b** as a colorless oil, which was converted to **15b**·HCl (3.2 g, 29%), colorless needles, mp 235—236°. *Anal.* Calcd. for $C_{25}H_{26}N_2O_4$·HCl: C, 66.00; H, 5.98; N, 6.16. Found: C, 65.73; H, 5.77; N, 5.88. NMR (in d_6-DMSO) δ: 5.20 (1H, d, J=2 Hz, C_1–H).

b) A solution of **16** (6.0 g) and benzylmethylamine (4.0 g) in methyl ethyl ketone (100 ml) was heated under nitrogen at 60° with stirring for 5 hr. After removal of the insoluble substance by filtration, the filtrate was evaporated *in vacuo* and the residue was extracted with 10% HCl (100 ml). The extract was treated with active charcoal and made alkaline with $NaHCO_3$. The resulting oily substance was extracted with AcOEt, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in MeOH (30 ml) and to the solution was added portionwise $NaBH_4$ (1.5 g) with stirring at 0°. After stirring at room temperature for 0.5 hr, the mixture was poured into ice-water (100 ml) and extracted with AcOEt (200 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was submitted to column chromatography on silica gel and eluted with acetone–benzene (1: 4). Evaporation of the first fraction gave **15a** as an oil, which was converted to the hydrochloride to give **15a**·HCl (1.1 g, 16%) as colorless needles. Further elution with the same eluant afforded **15b** as an oil, which was converted to **15b**·HCl (0.6 g, 9%).

***trans*-2,5-Diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (2a) (Table I)**——A solution of **11** (1.0 g) in MeOH (30 ml) was catalytically hydrogenated over 10% Pd-C (0.5 g) under atmospheric pressure at room temperature. After removal of the catalyst by filtration, 20% HCl–EtOH (5 ml) was added to the filtrate. Upon addition of ether (100 ml) to the solution, **2a** (0.54 g, 75%) deposited as colorless needles. NMR (in d_6-DMSO) δ: 4.60 (1H, d, J=8 Hz, C_1–H).

Catalytic Reduction of 10——A solution of **10** (1.0 g) in a mixture of water (10 ml), EtOH (5 ml) and conc. HCl (0.5 ml) was hydrogenated over PtO_2 (0.5 g) under atmospheric pressure at room temperature. After removal of the catalyst, to the filtrate was added ether (100 ml) and the resulting precipitate was filtered to give a mixture of **2a** and the *cis* isomer (**2b**) (0.6 g, 71%) as colorless needles, mp>300°. *Anal.* Calcd. for $C_{10}H_{14}N_2O_2$·2HCl·3/2H_2O: C, 40.82; H, 6.51; N, 9.52. Found: C, 41.14; H, 6.39; N, 9.25. NMR (in d_6-DMSO) δ: 4.68 (2/3H, d, J=3 Hz, C_1–H), 4.58 (1/3H, d, J=8 Hz, C_1–H).

***trans*-5-Amino-6-hydroxy-2-methylamino-1,2,3,4-tetrahydro-1-naphthalenol (2c) (Table I)**——A solution of **15a** (1.0 g) in MeOH (30 ml) was catalytically hydrogenated over 10% Pd-C (1.0 g) under atmospheric pressure at room temperature. After removal of the catalyst, to the solution was added the saturated ethereal solution of fumaric acid (10 ml). The solution was allowed to stand at room temperature. The resulting precipitate was collected by filtration to give **2c** (0.64 g, 82%) as colorless needles. NMR (in d_6-DMSO) δ: 2.53 (3H, s, NCH_3), 4.50 (1H, d, J=8 Hz, C_1–H).

***trans*-2-Substituted Amino-5-amino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol Derivatives (2d—r) (Table I)**——General procedure: A solution of the corresponding **12** (1.0 g) in MeOH (30 ml) was catalytically hydrogenated over 10% Pd-C (0.5 g) under atmospheric pressure at room temperature until theoretical amount of hydrogen was taken up. After removal of the catalyst, to the solution was added 20% HCl–EtOH (5 ml) and then the mixture was diluted with ether (100 ml). The resulting precipitate was filtered to give the hydrochlorides. Compounds **2h**, **2q** and **2r** were isolated as the fumarate by the conventional method.

6-Benzyloxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (17)——A mixture of **6** (35 g), benzyl chloride (22 g), anhydrous K_2CO_3 (13 g), KI (3.0 g), and DMF (350 ml) was heated with stirring at 80° for 3 hr. The mixture was poured into ice-water (1.5 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from EtOH to give **17** (42 g, 85%) as colorless prisms, mp 175—177°. *Anal.* Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.56; H, 5.01; N, 4.62.

6-Benzyloxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone Oxime (18)——To a stirred solution of **17** (18 g) in a mixture of MeOH (135 ml) and water (13 ml) was added NH_2OH·HCl (16.5 g) and K_2CO_3 (16.5 g). After being refluxed with stirring for 3 hr, the mixture was poured into water (200 ml). The resulting precipitate was filtered, washed with water, and recrystallized from MeOH to give **18** (16 g, 85%) as colorless needles, mp 181—183°. *Anal.* Calcd. for $C_{17}H_{16}NO_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.11; H, 5.10;

N, 8.88.

6-Benzyloxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-*p*-Toluenesulfonate (19)——To a stirred solution of **18** (16 g) in pyridine (50 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (19 g) in pyridine (20 ml). After stirring at room temperature for 3 hr, the mixture was poured into ice-water (500 ml). The resulting precipitate was filtered and recrystallized from benzene to give **19** (25 g, 96%) as colorless needles, mp 167—169°. *Anal.* Calcd. for $C_{24}H_{22}N_2O_6S$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.74; H, 4.58; N, 6.15.

2-Amino-6-benzyloxy-7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (20)——To a stirred solution of **19** (23 g) in dry benzene (200 ml) was added dropwise a cooled solution of EtOK, prepared from K (1.6 g) and abs. EtOH (70 ml), under nitrogen at 5°. The mixture was stirred at 5° for 4 hr and allowed to stand in a refrigerator overnight. After removal of the insoluble substance by filtration, the filtrate was acidified by adding conc. HCl (30 ml). The resulting precipitate was collected by filtration, washed with ether and dissolved in hot MeOH (500 ml). After treatment with charcoal, the solution was concentrated *in vacuo* to 200 ml and diluted with ether (200 ml). The resulting precipitate was collected by filtration to give **20**·HCl (9.0 g, 53%) as pale yellow leaves, mp 215—217°. *Anal.* Calcd. for $C_{17}H_{16}N_2O_4$·HCl: C, 58.54; H, 4.91; N, 8.03. Found: C, 58.60; H, 5.16; N, 7.83.

***trans*-2-Amino-6-benzyloxy-7-nitro-1,2,3,4-tetrahydro-1-naphthalenol (21)**——To a stirred solution of **20** (7.2 g) in MeOH (200 ml) was added in portions $NaBH_4$ (3.0 g) at 5°. After stirring for 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*. The residue was dissolved in 20% HCl–EtOH (30 ml) and diluted with ether (100 ml). The resulting precipitate was filtered to give **21**·HCl (7.0 g, 97%) as colorless crystalline powder, mp>300°. *Anal.* Calcd. for $C_{17}H_{18}N_2O_4$·HCl: C, 58.20; H, 5.46; N, 7.99. Found: C, 58.44; H, 5.51; N, 7.83. NMR (in d_6-DMSO) δ: 4.50 (1H, d, J=10 Hz, C_1–H).

***trans*-6-Benzyloxy-2-isopropylamino-7-nitro-1,2,3,4-tetrahydro-1-naphthalenol (22)**——To a stirred solution of **21** (3.5 g) in mixture of MeOH (50 ml) and acetone (20 ml) was added in portions $LiBH_3CN$·dioxane (3.5 g). After stirring for 5 hr at room temperature, the mixture was poured into water (200 ml) and made acidic with 10% HCl. The solution was then neutralized with $NaHCO_3$ and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 20% HCl–EtOH (20 ml) and diluted with ether (100 ml). The resulting precipitate was collected by filtration to give **22**·HCl (2.8 g, 72%) as colorless needles, mp 278—280°. *Anal.* Calcd. for $C_{20}H_{24}N_2O_4$·HCl: C, 61.14; H, 7.13; N, 6.41. Found: C, 61.13; H, 7.22; N, 6.27. NMR (in d_6-DMSO) δ: 4.70 (1H, d, J=8Hz, C_1–H).

***trans*-2,7-Diamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenol (23)**——Free base of **21**, prepared by neutralization of an aqueous solution of **21**·HCl (3.0 g) with $NaHCO_3$ followed by extraction with AcOEt (200 ml) and evaporation, was dissolved in MeOH (50 ml) and the solution was catalytically hydrogenated over 10% Pd-C (3.0 g) under atmospheric pressure at room temperature. After removal of the catalyst, to the filtrate was added a saturated ethereal solution of fumaric acid (10 ml). The solution was allowed to stand in a refrigerator. The resulting precipitate was collected by filtration to give **23** fumarate (1.1 g, 51%) as colorless needles, mp>300°. *Anal.* Calcd. for $C_{10}H_{14}N_2O_2 \cdot 1/2C_4H_4O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.25; H, 6.22; N, 11.05. NMR (in d_6-DMSO) δ: 4.40 (1H, d, J=8 Hz, C_1–H).

***trans*-7-Amino-6-hydroxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (24)**——A solution of **22**·HCl (2.8 g) in water (100 ml) was neutralized with $NaHCO_3$ and extracted with AcOEt (200 ml). Free base of **22** obtained by evaporation of the extract was dissolved in MeOH (50 ml) and the solution was catalytically hydrogenated over 10% Pd-C (2.0 g) under atmospheric pressure at room temperature. After removal of the catalyst, to the filtrate was added a saturated ethereal solution of fumaric acid (10 ml). The resulting precipitate was filtered to give **24**·fumarate (1.4 g, 66%) as colorless needles, mp 205—208°. *Anal.* Calcd. for $C_{13}H_{20}N_2O_2 \cdot 1/2C_4H_4O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 61.01; H, 7.31; N, 9.69. NMR (in d_6-DMSO) δ: 4.35 (1H, d, J=8 Hz, C_1–H).

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