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Synthesis of 2-(*N*-Substituted amino)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ol Derivatives

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trans-6-Hydroxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (**8a**), *trans*-6-hydroxy-2-(1-methyl-2-phenoxyethyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (**8b**) and *trans*-1,6-dihydroxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydronaphthalene-5-carboxamide (**9a**) were synthesized as a part of our search for useful cardiovascular agents. 2-(*N*-Substituted amino)-6-alkoxy-1,2,3,4-tetrahydronaphthalen-1-ols (**10**—**31**) having various substituents at the 5-, 6- and 7-positions of the naphthalene ring were prepared by a five-step sequence of reactions starting from 3,4-dihydro-1(2*H*)-naphthalenone derivatives (**36**). Furthermore 2-(*N*-substituted amino)-1-indanol derivatives (**33**) and 6-(*N*-substituted amino)-2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**34**, **35**) were obtained by the reductive alkylation of the corresponding amino alcohols with carbonyl compounds. These *N*-substituted amino alcohols (**8**—**35**) were tested for vasodilating activity in anesthetized dogs and for β-blocking activity using isolated guinea pig atrial preparations.

Keywords——β-adrenergic activity; vasodilator; conformationally restricted analog; 2-amino-1,2,3,4-tetrahydronaphthalen-1-ol; Neber rearrangement

Previously we synthesized a series of 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalen-1-ol derivatives (**2**) which are conformationally restricted analogs of adrenergic catecholamines (**1**), noradrenaline, adrenaline and isoproterenol.[1] Biological tests revealed that many of the *trans* isomers of **2** possess potent β-adrenoceptor stimulating activities. In view of the low activities exhibited by the subsequently synthesized two types of analogs, 6-amino-1,2-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol derivatives (**3**)[2] and 7,8-dihydroxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-1-ol (**4**),[3] the *trans*-diequatorial conformation[4] of the aminoethanol moiety fixed into a tetrahydronaphthalene skeleton appeared to represent the most favorable conformation for the interaction with β-adrenoceptors. These results led us to apply this method of modification to other adrenergic drugs having a phenylethanolamine structure. This paper is concerned with the synthesis and some biological activities of tetrahydronaphthalene congeners (**8a**, **8b**, **9a**) of nylidrin (**5**) and isoxsuprine (**6**), both of which are used as vasodilators, and labetalol (**7**),[5] an α-and β-blocker. Furthermore, a series of *trans*-6-alkoxy-2-aminonaphthalen-1-ol derivatives (**10**—**31**) was prepared as a part of our search for useful cardiovascular agents. Derivatives of 5-hydroxy-2-aminoindan-1-ol (**33**) and 2-hydroxy-6-aminobenzocyclohepten-5-ol (**34**, **35**) were also synthesized in order to investigate the influence of the ring size on the biological activity.

Chemistry

First, *trans*-6-hydroxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (**8a**) and *trans*-6-hydroxy-2-(1-methyl-2-phenoxyethyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (**8b**) were synthesized by the scheme shown in Chart 1. Thus, the Neber rearrangement of a tosyloxime (**38a**) and subsequent reduction of the resulting amino

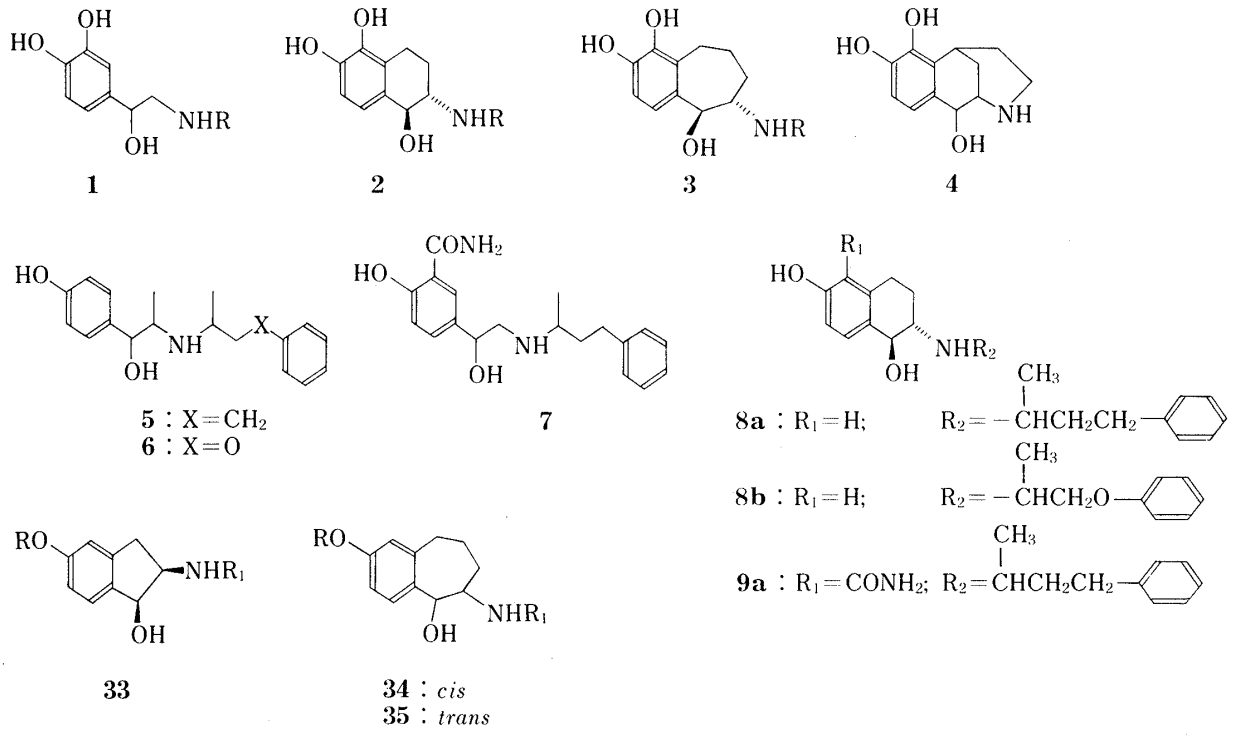


Fig. 1

ketone (**39a**) with sodium borohydride ($NaBH_4$) gave exclusively *trans*-2-amino-6-benzyloxy-1,2,3,4-tetrahydronaphthalen-1-ol (**40a**). The *trans* configuration of the aminoethanol moiety of **40a** was confirmed by the nuclear magnetic resonance (^{1}H-NMR) spectrum, which showed C_1–H at δ 4.60 as a doublet with a coupling constant (J) of 9 Hz. The reductive alkylation of **40a** with benzylacetone and phenoxyacetone in the presence of sodium cyanoborohydride ($NaBH_3CN$) afforded *trans*-6-benzyloxy-2-(1-methyl-3-phenylpropyl)-amino-1,2,3,4-tetrahydronaphthalen-1-ol (**10a**) and *trans*-6-benzyloxy-2-(1-methyl-2-phenoxyethyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (**10b**), respectively. These two compounds were debenzylated by catalytic hydrogenolysis to **8a** and **8b**. Several related compounds (**10c—10h**, Table I) were prepared by the reaction of **40a** with the corresponding carbonyl compounds and $NaBH_3CN$.

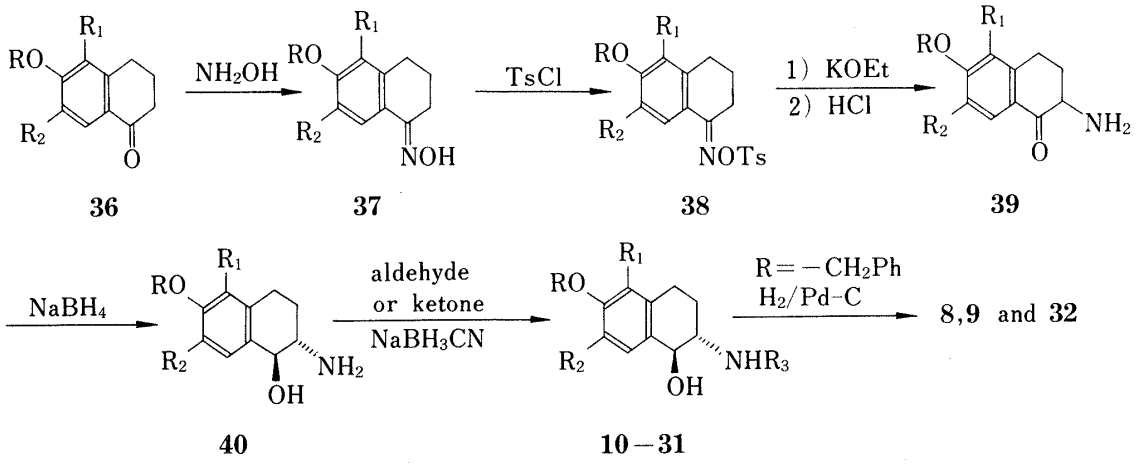
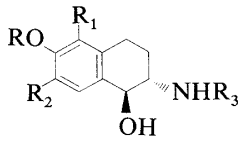


Chart 1

TABLE I. *trans*-2-(*N*-Substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (**8**—**32**)



Compd. No.	R	R_1	R_2	R_3	Yield (%)	Form	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δ J[a]
8a	H	H	H	$CH(CH_3)CH_2CH_2Ph$	89	Fumarate	185—187	$C_{20}H_{25}NO_2 \cdot C_4H_4O_4 \cdot \frac{1}{2}H_2O$	71.52 (71.17)	7.37 (7.19)	3.79 (3.67)	4.68 (9)
8b	H	H	H	$CH(CH_3)CH_2OPh$	86	Fumarate	184—186	$C_{19}H_{23}NO_3 \cdot C_4H_4O_4$	64.32 (64.12)	6.34 (6.31)	3.26 (3.52)	4.58 (9)
8c	H	H	H	$CH(CH_3)_2$	75	HCl	196—197	$C_{13}H_{19}NO_2 \cdot HCl$	60.57 (60.41)	7.82 (7.70)	5.44 (5.31)	4.70 (8)
9a	H	$CONH_2$	H	$CH(CH_3)CH_2CH_2Ph$	69	HCl	Amorphous	$C_{21}H_{26}N_2O_3 \cdot HCl$	64.52 (64.12)	6.96 (6.75)	7.17 (7.05)	4.85 (9)
9b	H	$CONH_2$	H	$CH(CH_3)_2$	75	HCl	>300	$C_{14}H_{20}N_2O_3 \cdot HCl$	55.90 (55.40)	7.04 (7.08)	9.32 (9.35)	4.70 (9)
10a	CH_2Ph	H	H	$CH(CH_3)CH_2CH_2Ph$	70	HCl	184—186	$C_{27}H_{31}NO_2 \cdot HCl$	74.03 (74.08)	7.35 (7.50)	3.20 (3.24)	4.80 (8)
10b	CH_2Ph	H	H	$CH(CH_3)CH_2OPh$	70	Oxalate	186—187	$C_{26}H_{29}NO_3 \cdot C_2H_2O_4$	68.14 (67.73)	6.33 (6.25)	2.84 (2.92)	4.70 (9)
10c	CH_2Ph	H	H	$CH(CH_3)_2$	80	HCl	198—200	$C_{20}H_{25}NO_2 \cdot HCl$	69.05 (69.23)	7.53 (7.44)	4.03 (3.80)	4.65 (9)
10d	CH_2Ph	H	H	Cyclohexyl	79	HCl	229—230	$C_{23}H_{29}NO_2 \cdot HCl$	71.21 (71.20)	7.80 (7.88)	3.61 (3.53)	4.75 (9)
10e	CH_2Ph	H	H	$CH(CH_3)CH_2CH_3$	85	HCl	215—217	$C_{21}H_{27}NO_2 \cdot HCl$	69.69 (69.61)	7.80 (7.63)	3.87 (3.80)	4.80 (9)

TABLE I. continued

Compd. No.	R	R_1	R_2	R_3	Yield (%)	Form	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δ J [a]
10f	CH_2Ph	H	H	$CH(CH_3)CH(CH_3)_2$	76	HCl	197—201	$C_{22}H_{29}NO_2 \cdot HCl \cdot 1/2H_2O$	68.65 (69.00)	8.12 (8.04)	3.64 (3.71)	4.80 (9)
10g	CH_2Ph	H	H	$CH(CH_3)CH_2Ph$	79	HCl	198—199	$C_{26}H_{29}NO_2 \cdot HCl$	73.65 (73.68)	7.13 (7.15)	3.30 (3.21)	4.80 (9)
10h	CH_2Ph	H	H	CH_2Ph	77	HCl	177—178	$C_{24}H_{25}NO_2 \cdot HCl$	72.80 (72.88)	6.62 (6.43)	3.54 (3.77)	4.84 (9)
11	CH_2Ph-(p-Cl)	H	H	$CH(CH_3)_2$	49	Fumarate	180—181	$C_{20}H_{24}ClNO_2 \cdot C_4H_4O_4$	62.40 (62.75)	6.11 (6.42)	3.03 (2.98)	4.65 (9)
12	CH_2Ph-(o-Cl)	H	H	$CH(CH_3)_2$	93	HCl	212—217	$C_{20}H_{24}ClNO_2 \cdot HCl$	62.83 (62.67)	6.59 (6.57)	3.66 (3.81)	4.75 (9)
13	CH_2Ph-(m-OCH_3)	H	H	$CH(CH_3)_2$	89	HCl	191—194	$C_{21}H_{27}NO_3 \cdot HCl$	66.74 (66.45)	7.47 (7.43)	3.71 (3.84)	4.75 (9)
14	CH_2CH_2Ph	H	H	$CH(CH_3)_2$	80	HCl	183—184	$C_{21}H_{27}NO_2 \cdot HCl$	69.69 (69.75)	7.80 (7.63)	3.87 (3.95)	4.80 (9)
15	CH_2CH_2-cyclohexyl	H	H	$CH(CH_3)_2$	89	HCl	209—210	$C_{21}H_{33}NO_2 \cdot HCl$	68.55 (68.67)	9.31 (9.43)	3.81 (3.72)	4.60 (9)
16	CH_3	H	H	$CH(CH_3)CH_2CH_2Ph$	75	HCl	186—187	$C_{21}H_{27}NO_2 \cdot HCl$	69.69 (69.55)	7.80 (7.61)	3.87 (3.75)	4.60 (8)
17	CH_2CH_3	H	H	$CH(CH_3)_2$	93	HCl	201—202	$C_{15}H_{23}NO_2 \cdot HCl$	63.03 (62.79)	8.46 (8.61)	4.90 (4.80)	4.65 (8)
18	$CH(CH_3)_2$	H	H	$CH(CH_3)_2$	47	HCl	175—177	$C_{16}H_{25}NO_2 \cdot HCl$	64.09 (63.98)	8.74 (8.65)	4.67 (4.60)	4.65 (8)
19	CH_2-$CH=CH_2$	H	H	$CH(CH_3)_2$	60	HCl	198—199	$C_{16}H_{23}NO_2 \cdot HCl$	64.52 (64.26)	8.12 (8.15)	4.71 (4.80)	4.52 (8)

TABLE I. continued

Compd. No.	R	R_1	R_2	R_3	Yield (%)	Form	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δ J[a)]
20	CH_2CH_2-OCH_2CH_3	H	H	$CH(CH_3)_2$	58	HCl	163—164	$C_{17}H_{27}NO_3 \cdot HCl$	61.90 (61.94)	8.56 (8.66)	4.25 (4.16)	4.65 (9)
21	$(CH_2)_3CH_3$	H	H	$CH(CH_3)_2$	40	HCl	186—188	$C_{17}H_{27}NO_2 \cdot HCl$	65.05 (65.73)	8.99 (8.85)	4.46 (4.50)	4.72 (8)
22	CH_2COO-CH_3	H	H	$CH(CH_3)_2$	31	HCl	173—175	$C_{16}H_{23}NO_4 \cdot HCl$	58.26 (58.40)	7.33 (7.18)	4.25 (4.19)	4.85 (9)
23a	CH_3	NO_2	H	$CH(CH_3)CH_2CH_2Ph$	68	HCl	235—237	$C_{21}H_{26}N_2O_4 \cdot HCl$	61.98 (61.91)	6.69 (6.62)	6.89 (6.96)	4.80 (8)
23b	CH_3	NO_2	H	$CH(CH_3)_2$	60	HCl	275—277	$C_{14}H_{20}N_2O_4 \cdot HCl$	53.08 (52.66)	6.68 (6.44)	8.85 (8.49)	4.64 (8)
23c	CH_3	NO_2	H	$CH(Ph)_2$	75	HCl	255—257	$C_{24}H_{24}N_2O_4 \cdot HCl$	65.37 (65.40)	5.72 (5.69)	6.36 (6.26)	4.90 (9)
24a	CH_3	NH_2	H	$CH(CH_3)CH_2CH_2Ph$	46	Fumarate	175—177	$C_{21}H_{28}N_2O_2 \cdot 1/2C_4H_4O_4$	69.32 (69.05)	7.59 (7.45)	7.03 (6.84)	4.82 (8)
24b	CH_3	NH_2	H	$CH(CH_3)_2$	55	Fumarate	218—220	$C_{14}H_{22}N_2O_2 \cdot C_4H_4O_4$	59.00 (58.78)	7.15 (7.07)	7.65 (7.29)	4.82 (8)
25	CH_3	$N(CH_3)_2$	H	$CH(CH_3)_2$	76	HCl	215—216	$C_{16}H_{26}N_2O_2 \cdot 2HCl \cdot H_2O$	52.03 (52.07)	8.19 (8.19)	7.59 (7.69)	4.80 (9)
26a	CH_3	H	NO_2	$CH(CH_3)CH_2CH_2Ph$	77	HCl	242—244	$C_{21}H_{26}N_2O_4 \cdot HCl$	61.98 (61.88)	6.69 (6.52)	6.89 (6.83)	4.56 (8)
26b	CH_3	H	NO_2	$CH(CH_3)_2$	45	HCl	279—280	$C_{14}H_{20}N_2O_4 \cdot HCl$	53.08 (52.78)	6.68 (6.80)	8.84 (8.68)	4.60 (8)
27	CH_3	H	NH_2	$CH(CH_3)CH_2CH_2Ph$	54	Fumarate	174—175	$C_{21}H_{28}N_2O_2 \cdot 1/2C_4H_4O_4$	69.32 (68.93)	7.59 (7.52)	7.03 (6.87)	4.80 (8)

TABLE I. continued

Compd. No.	R	R_1	R_2	R_3	Yield (%)	Form	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δ $J^{a)}$
28	CH_3	Cl	H	$CH(CH_3)_2$	78	HCl	260—261	$C_{14}H_{20}ClNO_2 \cdot HCl$	54.91 (54.60)	6.91 (6.93)	4.58 (4.60)	4.70 (8)
29	CH_3	CN	H	$CH(CH_3)_2$	91	HCl	262—264	$C_{14}H_{20}N_2O_2 \cdot HCl$	59.04 (59.08)	7.43 (6.95)	9.84 (9.43)	4.76 (8)
30a	CH_2Ph	$COOCH_3$	H	$CH(CH_3)CH_2CH_2Ph$	68	HCl	174—178	$C_{29}H_{33}NO_4 \cdot HCl$	70.22 (69.97)	6.91 (6.99)	2.82 (2.81)	4.80 (8)
30b	CH_2Ph	$COOCH_3$	H	$CH(CH_3)_2$	75	HCl	239—241	$C_{22}H_{27}NO_4 \cdot HCl$	65.10 (64.83)	6.95 (6.71)	3.45 (3.62)	4.80 (8)
31a	CH_2Ph	$CONH_2$	H	$CH(CH_3)CH_2CH_2Ph$	61	HCl	215—218	$C_{28}H_{32}N_2O_3 \cdot HCl$	69.91 (70.11)	6.91 (7.15)	5.82 (5.69)	4.75 (9)
31b	CH_2Ph	$CONH_2$	H	$CH(CH_3)_2$	75	HCl	223—225	$C_{21}H_{26}N_2O_3 \cdot HCl$	64.52 (64.77)	6.92 (6.74)	7.17 (7.38)	4.70 (9)
32a	H	$COOCH_3$	H	$CH(CH_3)CH_2CH_2Ph$	51	HCl	175—179	$C_{22}H_{27}NO_4 \cdot HCl$	65.09 (65.65)	6.95 (6.84)	3.45 (3.17)	4.80 (8)
32b	H	$COOCH_3$	H	$CH(CH_3)_2$	77	HCl	237—239	$C_{15}H_{21}NO_4 \cdot HCl$	57.05 (57.08)	7.02 (7.16)	4.44 (4.26)	4.75 (9)

a) Coupling constants J are expressed in Hz.

Subsequently, the preparation of *trans*-1,6-dihydroxy-2-(1-methyl-3-phenylpropyl)-amino-1,2,3,4-tetrahydronaphthalene-5-carboxamide (**9a**), a cyclic analog of labetalol (**7**), was undertaken. Our inital approach to obtain **9a** by the amidation of methyl 6-benzyloxy-1-hydroxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydro-5-naphthoate (**30a**), which was prepared from methyl 6-benzyloxy-1-oxo-1,2,3,4-tetrahydro-5-naphthoate (**36s**),[7] was unsuccessful. Therefore **36s** was converted to 5-carbamoyl-1-tetralone (**36t**) and **36t** was led to **9a** according to the sequence of reactions illustrated in Chart 1. By the same procedure, some analogs, **8c**, **9b**, **32a** and **32b** (Table I) were prepared.

Our investigations so far had revealed that some of the 6-alkoxy derivatives of 2-alkylamino-1,2,3,4-tetrahydronaphthalen-1-ol possess considerable adrenoceptor activities in spontaneously hypertensive rats (SHR), although they are less potent than the 6-hydroxy analogs. This fact further prompted us to synthesize a variety of 6-alkoxy derivatives (**11**—**29**, Table I).

Several substituted 1-tetralones (**36b**—**r**), the starting materials for the synthesis, were prepared by the methods illustrated in Chart 2.

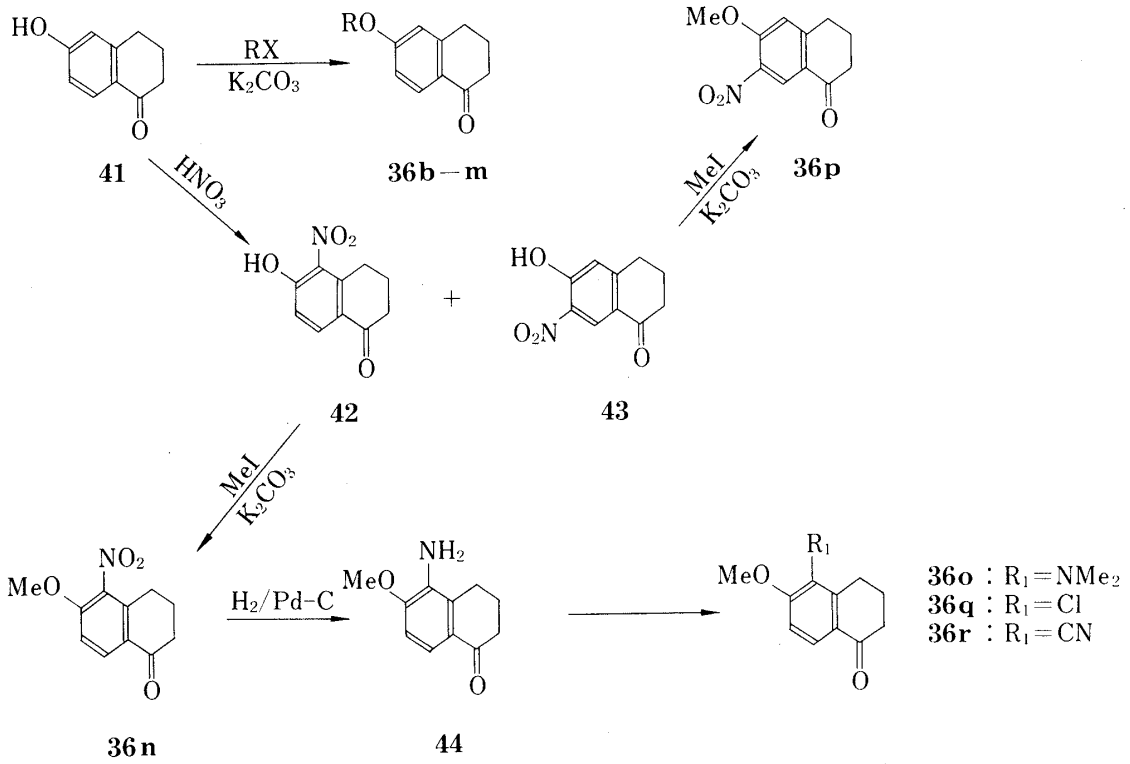
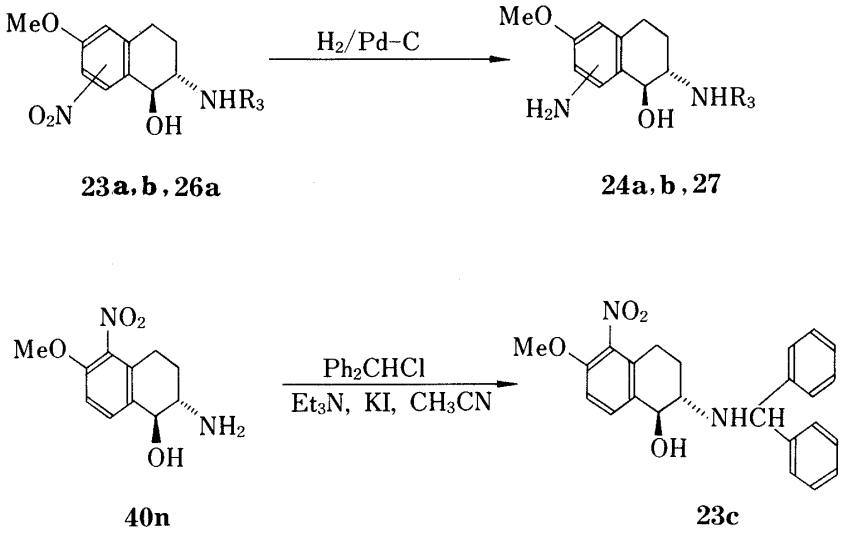


Chart 2

Thus, a series of 6-alkoxy-1-tetralones (**36b**—**m**) was prepared by the reaction of 6-hydroxytetralone (**41**) with corresponding alkyl halides. 6-Methoxy-5- and 7-nitro-1-tetralones (**36n** and **36p**) were obtained by methylation of **42**[8] and **43**,[8] respectively. Compound **36n** was led to 5-dimethylamino-6-methoxy-1-tetralone (**36o**) by reduction of a nitro group, affording the 5-amino derivative (**44**), followed by methylation.[9] Furthermore, 5-chloro- (**36q**) and 5-cyano-1-tetralone (**36r**) were obtained by the Sandmeyer reaction of **44**.

These tetralones (**36b**—**r**) were converted to 2-isopropylamino- (**11**—**15**, **17**—**22**, **23b**, **25**, **26b**, **28** and **29**, Table I) and 2-(1-methyl-3-phenylpropyl)aminotetrahydronaphthalenols (**16**, **23a** and **26a**, Table I). The 5- and 6-nitro compounds (**23a**, **23b** and **26a**) were led to the corresponding amino derivatives (**24a**, **24b** and **27**). The 2-benzhydrylamino compound (**23c**)

was obtained by alkylation of 2-amino-5-nitro-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (**40n**) with benzhydryl chloride.

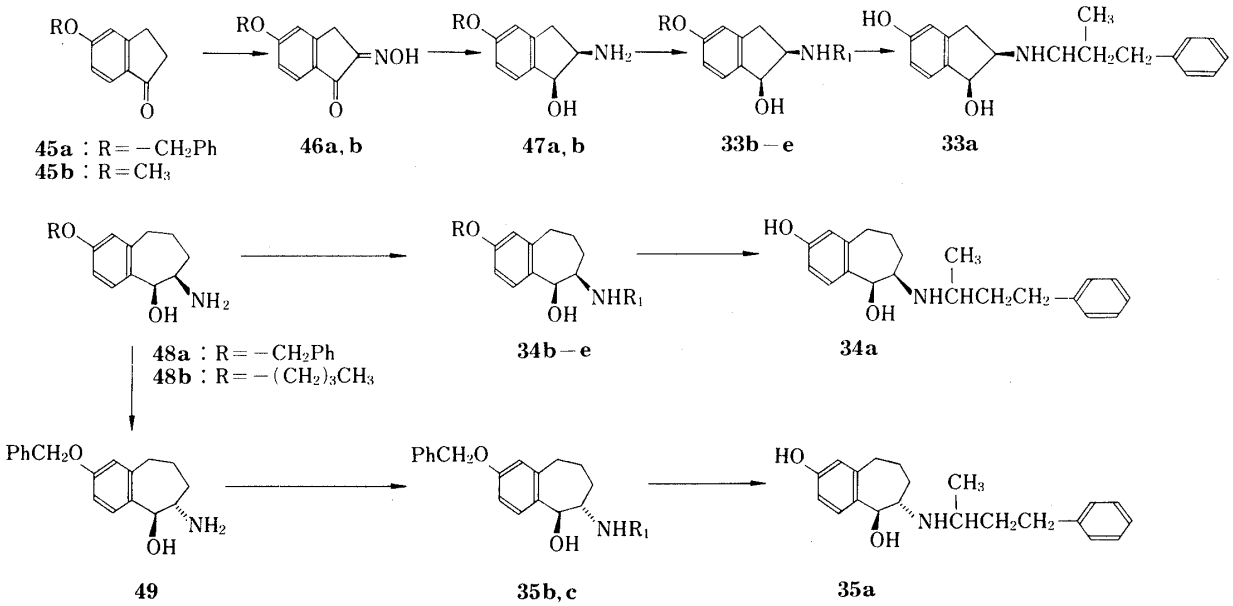


23a,b,26a **24a,b,27**

40n **23c**

Chart 3

The synthesis of indan and benzocycloheptene derivatives (**33**—**35**, Tables II and III) was performed by the following methods (Chart 4). 5-Methoxy-2-hydroxyimino-1-indanone (**46b**) was reduced with lithium aluminum hydride ($LiAlH_4$) or by catalytic hydrogenation to an amino alcohol (**47b**). Its configuration with respect to the 1,2-amino alcohol moiety was concluded to be *cis* on the basis of the melting point reported in the literature.[10] The *cis*-5-benzyloxy analog (**47a**) was prepared by a similar procedure. Compounds **47a** and **47b** were led to the *N*-alkyl derivatives (**33b**—**e**) by reductive alkylation, and **33b** was further led to **33a** by hydrogenolysis.



45a : R = $-CH_2Ph$
45b : R = CH_3

46a,b **47a,b** **33b—e** **33a**

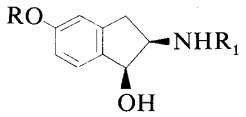
48a : R = $-CH_2Ph$
48b : R = $-(CH_2)_3CH_3$

34b—e **34a**

49 **35b,c** **35a**

Chart 4

TABLE II. *cis*-2-(*N*-Substituted amino)indan-1-ols (**33a—e**)



Compd. No.	R	R_1	Yield (%)	Form	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δJ [a]
33a	H	$CH(CH_3)CH_2CH_2Ph$	47	Fumarate	192—195	$C_{19}H_{23}NO_2 \cdot 1/2C_4H_4O_4$	70.96 (71.01)	7.09 (7.27)	3.94 (3.75)	5.18 (6)
33b	CH_2Ph	$CH(CH_3)CH_2CH_2Ph$	98	Fumarate	200—201	$C_{26}H_{29}NO_2 \cdot 1/2C_4H_4O_4$	75.48 (75.60)	7.01 (7.22)	3.14 (2.92)	5.30 (6)
33c	CH_2Ph	$CH(CH_3)_2$	39	HCl	197—198	$C_{19}H_{23}NO_2 \cdot HCl$	68.35 (68.29)	7.25 (7.42)	4.20 (3.97)	5.28 (6)
33d	CH_3	$CH(CH_3)CH_2CH_2Ph$	93	HCl	174—178	$C_{20}H_{25}NO_2 \cdot HCl$	69.05 (68.95)	7.53 (7.39)	4.03 (3.97)	5.35 (5.5)
33e	CH_3	$CH(CH_3)_2$	28	HCl	184—187	$C_{13}H_{19}NO_2 \cdot HCl$	60.57 (60.84)	7.82 (7.87)	5.43 (5.29)	5.34 (5.5)

a) Coupling constants *J* are expressed in Hz.

On the other hand, *cis*-6-amino-2-benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**48a**) was prepared from 2-benzyloxy-6,7,8,9-tetrahydrocyclohepten-5-one by the method of Khanna.[11] By a similar procedure, the *cis*-2-butoxy analog (**48b**) was prepared. Compound **48a** was converted to the *trans* isomer (**49**) employing essentially the same procedure as previously described for the 1,2-dibenzyloxy[2] and 2,3-dibenzyloxy analogs.[11] The *cis*- and *trans*-amino alcohols (**48**, **49**) were led to the 6-alkylamino derivatives (**34b—e**, **35b**, **c**) by reductive alkylation. The benzyloxy compounds (**34b**, **35b**) were debenzylated to 2-hydroxy-6-(*N*-substituted amino)benzocycloheptenols (**34a**, **35a**).

Biological Tests

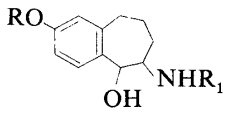
Compounds in Tables I—III were tested for β-blocking and peripheral vasodilating activities.

In order to test the β-blocking activity, isolated guinea pig atrial preparations were used. In brief, an isolated guinea pig atrial preparation was suspended in a 40 ml bath containing Krebs–Henseleit solution bubbled through with a 95% O_2 and 5% CO_2 gas mixture at 30 °C. One end of the preparation was fixed to the bath, and the other end was fixed to a strain-gauge transducer (Nihon Kohden, SB-1T) with threads to record contraction. Beating rate was recorded with a cardiotachometer (Nihon Kohden RT-2) triggered by signals of contraction.

After a stabilization period of about 60 min, isoproterenol was applied to the bath to give a final concentration of 2.5×10^{-8} M, and the increase in beating rate was observed for 3 min. After washing and another stabilization period of 40 to 60 min, a solution of test compound in physiological saline was applied at a final concentration of 10^{-6} M. Five minutes later, the preparation was again exposed to 2.5×10^{-8} M of isoproterenol for 3 min. β-Blocking activity was expressed as percent inhibition of the increase in beating rate due to isoproterenol after, as compared with that before, applying a test compound. Furthermore, direct cardiac action of test compounds was evaluated in terms of the percent change in beating rate during a period of 5 min when only a test compound was applied.

Vasodilating activity was tested in anesthetized dogs. In brief, mongrel dogs of either sex

TABLE III. 6-(*N*-Substituted amino)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**33**—**34**)



Compd. No.	R	R_1	Yield (%)	Form	mp (°C)	Formula	Analysis Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δJ[a]
34a (*cis*)	H	$CH(CH_3)CH_2CH_2Ph$	73	Fumarate	215—217	$C_{21}H_{27}NO_2 \cdot 1/2C_4H_4O_4$	68.00 (67.74)	7.08 (7.03)	3.17 (3.21)	4.82 (0)
34b (*cis*)	CH_2Ph	$CH(CH_3)CH_2CH_2Ph$	48	Fumarate	195—197	$C_{28}H_{33}NO_2 \cdot 1/2C_4H_4O_4$	76.08 (75.78)	7.45 (7.39)	2.96 (3.01)	4.80 (0)
34c (*cis*)	CH_2Ph	$CH(CH_3)_2$	65	HCl	181—183	$C_{21}H_{27}NO_2 \cdot HCl$	69.69 (69.46)	7.80 (7.55)	3.87 (3.93)	4.70 (2)
34d (*cis*)	$(CH_2)_3$-CH_3	$CH(CH_3)CH_2CH_2Ph$	45	Fumarate	209—210	$C_{25}H_{35}NO_2 \cdot 1/2C_4H_4O_4$	73.77 (73.92)	8.46 (8.65)	3.19 (3.16)	4.80 (2)
34e (*cis*)	$(CH_2)_3$-CH_3	$CH(CH_3)_2$	80	HCl	94—95	$C_{18}H_{29}NO_2 \cdot HCl$	65.93 (65.76)	9.22 (9.11)	4.27 (4.30)	4.65 (2)
35a (*trans*)	H	$CH(CH_3)CH_2CH_2Ph$	41	Fumarate	203—207	$C_{21}H_{27}NO_2 \cdot \frac{1}{2}C_4H_4O_4 \cdot \frac{1}{2}H_2O$	70.38 (70.47)	7.70 (7.61)	3.57 (3.66)	4.85 (6)
35b (*trans*)	CH_2Ph	$CH(CH_3)CH_2CH_2Ph$	75	Fumarate	179—181	$C_{28}H_{33}NO_2 \cdot \frac{1}{2}C_4H_4O_4 \cdot \frac{1}{2}H_2O$	74.97 (74.93)	7.13 (7.21)	2.92 (2.95)	4.84 (9)
35c (*trans*)	CH_2Ph	$CH(CH_3)_2$	84	Fumarate	183—184	$C_{21}H_{27}NO_2 \cdot \frac{1}{2}C_4H_4O_4 \cdot H_2O$	68.80 (69.16)	7.78 (7.50)	3.49 (3.50)	4.75 (10)

a) Coupling constants *J* are expressed in Hz.

(10—15 kg) were anesthetized with sodium pentobarbital (30 mg/kg, *i.v.*). After incision of the skin, the vertebral, carotid and femoral arteries were exposed, and probes of an electromagnetic flowmeter (Nihon Kohden, MF-46) were placed around these arteries in order to measure the blood flow of each artery. Simultaneously, systemic blood pressure was measured

TABLE IV. β-Adrenergic Blocking Activity

Compd.	β-Activity (10^{-6} M)	
	% Change in beating rate	% Inhibition of isop. (2.5×10^{-8} M) induced tachycardia
8a	+36±5	−66± 3
8b	+15±4	−31± 7
9a	+52±4	−80± 5
23a	+20±9	−27± 6
Practolol	+0.9±0.9	−26±10
Propranolol	−5.8±1.6	−62±11

Values are the means±S.E. of three preparations.

TABLE V. Vasodilating Activity

Compd.	Dose (*iv*) mg/kg	HR (%)				SBP (%)				VBF (%)				CBF (%)				FBF (%)			
		1′	5′	10′	60′	1′	5′	10′	60′	1′	5′	10′	60′	1′	5′	10′	60′	1′	5′	10′	60′
8a	0.1	+27	+29	+33	+23	−13	−13	−26	−19	+134	+206	+206	+200	+124	+202	—	+241	+21	−33	+21	+21
	0.01	+12	+17	+27	+1	−13	−15	−16	−22	+185	+219	+251	+136	+58	+79	—	+216	−17	+17	+25	−7
8b	1.0	+24	+24	+27	+7	−31	−14	−13	−7	+24	−6	0	—	+63	+53	+43	—	+131	+22	−12	—
	0.5	+8	+8	+7	—	−35	−7	−5	—	+124	−15	−23	—	+48	+3	−1	—	+84	−2	+1	—
10a	0.1	−1	+2	+5	+6	−1	−2	−1	—	+13	+35	+70	+56	+5	+16	—	—	−5	+6	+2	+24
23a	0.1	+30	+37	+38	+32	−8	+3	−1	+1	+75	+217	+208	+142	—	—	—	—	−17	+34	+50	+150
24a	0.1	+9	+9	+15	+15	−6	−11	−14	−27	+15	+35	+45	+15	—	—	—	—	−33	+17	+8	—
5	0.1	+11	+5	+3	—	−26	−11	−4	—	+38	−2	—	—	+20	+13	+15	+7	+11	+5	+15	—

Values are the means of three trials.
HR, heart rate; SBP, blood pressure; VBF, vertebral blood flow; CBF, carotid blood flow; FBF, femoral blood flow.

with an electromanometer (Nihon Kohden, MP-24T) *via* a polyethylene cannula inserted into the contralateral femoral artery, and the heart rate was registered with a cardiotachometer (Nihon Kohden, RT-2) triggered by blood pressure pulses. A test compound was intravenously injected into the femoral vein, and changes in arterial blood flow, blood pressure and heart rate were followed for 60 min after the administration.

A fairly high β-adrenergic blocking activity was found with four compounds, **8a**, **8b**, **9a** and **23a** (Table IV). A cyclic analog (**9a**) of labetalol was the most potent in β-blocking action, but it showed intrinsic cardiac stimulation, as seen in an increase in beating rate. Such cardiac stimulation was also noted with the other three compounds (**8a**, **8b** and **23a**).

The series of 6-alkoxy derivatives (**10**—**31**, Table I) shows relatively weak activity in these β-adrenergic tests *in vitro* compared with the 6-hydroxy analogs, **8** and **9**. However, some of the compounds of this series, **10c**—**g**, **13**, **20** and **21**, showed hypotensive activity as indicated by a decrease of 20—30 mmHg in blood pressure in SHR at 1 and 3 h after oral administration of 30 mg/kg (data not shown). From the fact that tachycardia in SHR was also observed with these compounds, this hypotensive effect is considered to be mainly due to β-adrenergic stimulation.

The β-stimulating action appeared to be strengthened in these 2-amino-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ol derivatives, as compared with the corresponding linear chain analogs, in accord with our previous observation in catecholamine analogs.[1)]

In the vasodilating test, **8a** (nylidrin analog), **8b** (isoxsuprine analog), **10a**, **23a** and **24a** were found to have a fairly high vasodilating activities, especially in the vertebral area, with **8b** being relatively weak, as shown in Table V. Among them, compound **8a** was the most active, and the vertebral blood flow (VBF) was increased by almost 200% at 5, 10 and 60 min after administration of 0.1 mg/kg, with a decrease in blood pressure and an increase in heart rate.

Most of the indan and benzocyclohepten (**33**—**35**) derivatives showed very weak β-adrenergic activity *in vitro* and in SHR, and weak vasodilating activity in dogs.

Experimental[12)]

6-Alkoxy-3,4-dihydro-1(2*H*)-naphthalenones (36b—m)——A mixture of **41**[6)] (0.1 mol), alkyl halide[13)] (0.11 mol), dimethylformamide (DMF) (100 ml) and K_2CO_3 (16 g) was stirred for 3 h at 100 °C. The reaction mixture was poured into water (500 ml) and extracted with AcOEt (100 ml × 3). The extract was washed with 1 N HCl (50 ml × 2) and water (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from EtOH. *p*-Chlorobenzyloxynaphthalenone (**36b**), colorless prisms (91%), mp 92—94 °C, *Anal.* Calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.72. Found: C, 70.99; H, 5.63. *o*-Chlorobenzyloxynaphthalenone (**36c**). colorless prisms (93%), mp 112—114 °C, *Anal.* Calcd for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.72. Found: C, 71.01; H, 5.58. *m*-Methoxybenzyloxynaphthalenone (**36d**), colorless prisms (90%), mp 109—110 °C, *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.64; H, 6.40. Phenethyloxynaphthalenone (**36e**), syrup (88%), IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). Cyclohexylethoxynaphthalenone (**36f**), syrup (100%), IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). Ethoxynaphthalenone (**36h**), syrup (85%), IR ν_{max}^{neat} cm^{-1}: 1685 (C=O). Isopropoxynaphthalenone (**36i**), syrup (79%), IR ν_{max}^{neat} cm^{-1}: 1685 (C=O). Allyloxynaphthalenone (**36j**), syurp (84%), IR ν_{max}^{neat} cm^{-1}: 1675 (C=O). Ethoxyethoxynaphthalenone (**36k**), syrup (718), IR ν_{max}^{neat} cm^{-1}: 1680 (C=O). Butoxynaphthalenone (**36l**), syrup (85%), IR ν_{max}^{neat} cm^{-1}: 1680 (C=O). Ethoxycarbonylmethoxynaphthalenone (**36m**), colorless prisms (76%), mp 115—118 °C, *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.40; H, 6.71.

6-Methoxy-5- and 7-Nitro-3,4,-dihydro-1(2*H*)-naphthalenone (36n and 36p)——A mixture of **42** (0.1 mol), CH_3I (0.5 mol), DMF (100 ml) and K_2CO_3 (20 g) was stirred for 3 h at 100 °C. The reaction mixture was poured into water (500 ml) and extracted with AcOEt (100 ml). The extract was washed with 1 N HCl (50 ml) and water (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from EtOH to give **36n** (86%) as pale yellow prisms, mp 166—167 °C. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.60; H, 4.88; N, 6.03. In a similar manner **36p** was prepared from **43**, pale yellow prisms, yield 97%, mp 181—183 °C. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.88; H, 4.77; N, 6.32.

5-Amino-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (44)——A solution of **36n** (34 g) in MeOH (500 ml) was subjected to catalytic hydrogenation over 5% Pd-C (10 g) under atmospheric pressure at room temperature until the absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to

give **44** as an oily residue, which was led to the hydrochloride (**44**·HCl, 32.5 g, 93%) by treatment with 20% HCl–EtOH (50 ml) followed by dilution with ether (100 ml), mp 207—210 °C. *Anal.* Calcd for $C_{11}H_{13}NO_2 \cdot HCl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.77; H, 6.43; N, 6.03.

5-Dimethylamino-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (36o)——Free base of **44**, which was prepared by neutralization of **44**·HCl (23 g) with 1 N NaOH (excess), was dissolved in $CHCl_3$ (200 ml). Pyridine (20 ml) was added to the solution, then $(CF_3CO)_2O$ (25 ml) was added dropwise with stirring at 5 °C. Stirring was continued for 30 min at room temperature, then the reaction mixture was washed with water (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization of the residue from ether gave 6-methoxy-5-trifluoroacetylamino-3,4-dihydro-1(2*H*)-naphthalenone (21 g, 72%) as colorless crystals, mp 105—107 °C. *Anal.* Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.02; H, 3.95; N, 4.96. KOH (18 g) and CH_3I (45 g) were added to a solution of this compound (21 g) in acetone (120 ml), and the mixture was stirred for 3 h then concentrated *in vacuo*. The residue was taken up in 50% EtOH (100 ml), and the mixture was stirred for 1 h, poured into water (200 ml) and extracted with $CHCl_3$ (100 ml × 2). The extract was washed with water (30 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 20% HCl–EtOH (50 ml) and diluted with ether (300 ml). The resulting precipitate was collected by filtration to give 6-methoxy-5-methylamino-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride (13 g, 55%) as colorless needles, mp 198—200 °C. *Anal.* Calcd for $C_{12}H_{15}NO_2 \cdot HCl$: C, 59.63; H, 6.67; N, 5.80. Found: C, 59.71; H, 6.85; N, 5.66. This compound (13 g) was added to a mixture of K_2CO_3 (20 g), CH_3I (20 g) and EtOH (200 ml). The whole was heated at reflux for 5 h, then cooled, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 ml), washed with water (100 ml × 2), dried (Na_2SO_4) and concentrated *in vacuo* to give **36o** (10.4 g, 95%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (C=O).

5-Chloro-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (36q)——A solution of $NaNO_2$ (4.5 g) in water (15 ml) was added dropwise to a solution of **44**·HCl (15 g) in 5% HCl (250 ml) with stirring at 0 °C. The resulting solution was added dropwise to a stirred solution of CuCl (15 g) in conc. HCl (120 ml) at 0 °C. When the addition was complete, the solution was stirred at room temperature for 1 h. The mixture was poured into water (300 ml) and extracted with AcOEt (100 ml × 2). The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from MeOH to give **36q** (8.5 g, 61%) as colorless needles, mp 134—135 °C. *Anal.* Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.77; H, 5.10.

6-Methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-5-carbonitrile (36r)——A solution of $NaNO_2$ (8.1 g) in water (20 ml) was added dropwise to a solution of **44**·HCl (22 g) in 5% HCl (250 ml) with stirring at 0 °C. The resulting solution was added dropwise to a stirred mixture of $CuSO_4$ (34 g), KCN (38 g) and water (120 ml) at 0 °C. The mixture was stirred for 1 h and worked up as described above to give **36r** (12 g, 62%) as colorless needles, mp 178—180 °C. *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.47; H, 5.30; N, 6.81.

6-Benzyloxy-1-oxo-1,2,3,4-tetrahydronaphthalene-5-carboxamide (36t)——A solution of ethyl 6-benzyloxy-1-oxo-1,2,3,4-tetrahydronaphthalene-5-carboxylate (**36s**, 48 g)[7] in MeOH (200 ml) was treated with 10 N NaOH (100 ml). The mixture was allowed to stand for 1 h at room temperature, then acidified with conc. HCl to give 6-benzyloxy-1-oxo-1,2,3,4-tetrahydro-5-naphthoic acid (27 g). A solution of this acid (27 g) and PCl_5 (22.7 g) in benzene (200 ml) was heated under reflux for 1 h, then concentrated *in vacuo* and the residue was dissolved in dioxane (200 ml). NH_3 was bubbled through the resulting solution for 1 h at room temperature, then the solution was poured into water (500 ml), and extracted with AcOEt (300 ml). The extract was washed with water (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from AcOEt to give **36t** (20 g, 75%) as colorless crystals, mp 192—194 °C. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.95; H, 5.66; N, 4.58.

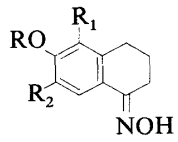
3,4-Dihydro-1(2*H*)-naphthalenone Oximes (37, Table VI)——General Procedure: K_2CO_3 (0.2 mol) and $NH_2OH \cdot HCl$ (0.4 mol) were added to a solution of naphthalenone derivative (**36**, 0.1 mol) in MeOH (200 ml) and water (20 ml). The mixture was refluxed for 3 h with stirring, then cooled and poured into water (500 ml). The resulting precipitate was collected by filtration, washed with water and recrystallized from 50% MeOH to give **37** as colorless crystals.

3,4-Dihydro-1(2*H*)naphthalenone *O*-Tosyloximes (38, Table VII)——General Procedure: *p*-Toluenesulfonyl chloride (0.2 mol) was added portionwise to an ice-cooled solution of **37** (0.1 mol) in pyridine (100 ml). After the addition was complete, the mixture was stirred for 30 min at 5 °C and for a further 1 h at room temperarure, then poured into ice-water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from MeOH or $CHCl_3$–MeOH to give **38** as colorless crystals.

2-Amino-3,4-dihydro-1(2*H*)-naphthalenones (39, Table VIII)——General Procedure: A solution of KOEt, prepared from K (0.055 mol) and abs. EtOH (30 ml), was added to a chilled solution of **38** (0.05 mol) in benzene (300 ml) under nitrogen. When the addition was complete, the reaction mixture was stirred for 5 h and allowed to stand for 1 week in a refrigerator. The deposited insoluble substance was removed by filtration, and conc. HCl (25 ml) was added to the filtrate. The resulting crystals were collected by filtration and recrystallized from EtOH (200 ml) to give **39**·HCl as colorless needles. In the cases of **39f** and **39o**, where the hydrochlorides failed to crystallize, the conc. HCl layer was separated and the benzene layer was extracted with 10% HCl (20 ml × 3). The combined acidic layer was evaporated to dryness and the residue was used for the subsequent step without purification.

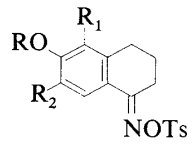
***trans*-2-Amino-1,2,3,4-tetrahydronaphthalen-1-ols (40, Table IX)**——General Procedure: A stirred solution of **39**.

TABLE VI. 3,4-Dihydro-1(2*H*)-naphthalenone Oximes (**37**)



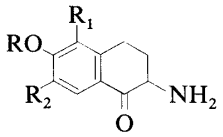
Compd. No.	R	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
37a	CH_2Ph	H	H	97	153—155	$C_{17}H_{17}NO_2$	76.38 (76.00)	6.41 (6.25)	5.24 (5.12)
37b	CH_2Ph-(*p*-Cl)	H	H	98	146—147	$C_{17}H_{16}ClNO_2$	67.66 (67.81)	5.35 (5.09)	4.64 (4.53)
37c	CH_2Ph-(*o*-Cl)	H	H	99	175—177	$C_{17}H_{16}ClNO_2$	67.66 (67.41)	5.35 (5.33)	4.64 (4.69)
37d	CH_2Ph-(*m*-OCH_3)	H	H	96	128—130	$C_{18}H_{19}NO_3$	72.70 (72.60)	6.44 (6.49)	4.71 (4.69)
37e	$(CH_2)_2$-Ph	H	H	33	97—98	$C_{18}H_{19}NO_2$	76.84 (76.59)	6.81 (6.63)	4.98 (4.71)
37f	$(CH_2)_2$-cyclohexyl	H	H	44	120—121	$C_{18}H_{25}NO_2$	75.22 (75.40)	8.77 (8.84)	4.87 (4.70)
37h	CH_2CH_3	H	H	80	148—149	$C_{12}H_{15}NO_2$	70.22 (70.06)	7.37 (7.41)	6.82 (6.84)
37i	$CH(CH_3)_2$	H	H	95	122—123	$C_{13}H_{17}NO_2$	71.20 (71.05)	7.82 (7.58)	6.39 (6.11)
37j	$CH_2CH=CH_2$	H	H	90	110—111	$C_{13}H_{15}NO_2$	71.86 (71.58)	6.92 (6.70)	6.45 (6.09)
37k	$(CH_2)_2$-OCH_2CH_3	H	H	87	83—85	$C_{14}H_{19}NO_3$	67.44 (67.50)	7.68 (7.56)	5.62 (5.40)
37l	$(CH_2)_3$-CH_3	H	H	74	106—108	$C_{14}H_{19}NO_2$	72.07 (71.88)	8.21 (8.06)	6.00 (5.72)
37m	CH_2COO-CH_2CH_3	H	H	85	142—143	$C_{14}H_{17}NO_4$	63.86 (63.70)	6.51 (6.34)	5.32 (5.06)
37n	CH_3	NO_2	H	85	182—184	$C_{11}H_{12}N_2O_4$	55.93 (55.60)	5.12 (5.10)	11.86 (11.73)
37o	CH_3	$N(CH_3)_2$	H	95	175—177	$C_{13}H_{18}N_2O_2$	66.64 (66.39)	7.74 (7.46)	11.96 (11.59)
37p	CH_3	H	NO_2	100	158—160	$C_{11}H_{12}N_2O_4$	55.93 (55.51)	5.12 (5.71)	11.86 (11.68)
37q	CH_3	Cl	H	90	192—194	$C_{11}H_{12}ClNO_2$	51.67 (51.44)	4.70 (4.61)	5.48 (5.60)
37r	CH_3	CN	H	81	220—222	$C_{12}H_{12}N_2O_2$	66.65 (66.87)	5.59 (5.33)	12.96 (13.01)
37t	CH_2Ph	$CONH_2$	H	95	244—246	$C_{18}H_{18}N_2O_3$	69.66 (69.87)	5.85 (5.56)	9.03 (8.97)

TABLE VII. 3,4-Dihydro-1(2*H*)-naphthalenone *O*-Tosyloximes (**38**)



Compd. No.	R	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
38a	CH_2Ph	H	H	87	144—146	$C_{24}H_{23}NO_4S$	68.40 (68.10)	5.50 (5.42)	3.33 (3.08)
38b	CH_2Ph (*p*-Cl)	H	H	86	120—121	$C_{24}H_{22}ClNO_4S$	63.23 (63.11)	4.86 (4.58)	3.07 (2.83)
38c	CH_2Ph (*o*-Cl)	H	H	90	134—136	$C_{24}H_{22}ClNO_4S$	63.23 (62.99)	4.86 (4.53)	3.07 (2.90)
38d	CH_2Ph-(*m*-OCH_3)	H	H	95	99—100	$C_{25}H_{25}NO_5S$	66.50 (66.58)	5.58 (5.58)	3.10 (3.10)
38e	$(CH_2)_2$-Ph	H	H	68	124—125	$C_{25}H_{25}NO_4S$	68.95 (68.78)	5.79 (5.54)	3.22 (3.09)
38f	$(CH_2)_2$-cyclohexyl	H	H	93	87—89	$C_{25}H_{31}NO_4S$	68.00 (67.71)	7.08 (7.26)	3.17 (3.11)
38h	CH_2CH_3	H	H	92	120—123	$C_{19}H_{21}NO_4S$	63.49 (63.40)	5.89 (5.92)	3.90 (3.87)
38i	$CH(CH_3)_2$	H	H	94	125—127	$C_{20}H_{23}NO_4S$	64.33 (64.47)	6.21 (6.50)	3.75 (2.57)
38j	$CH_2CH=CH_2$	H	H	85	103—104	$C_{20}H_{21}NO_4S$	64.68 (64.44)	5.70 (5.73)	3.77 (3.59)
38k	$(CH_2)_2$-OCH_2CH_3	H	H	93	83—85	$C_{21}H_{25}NO_5S$	62.52 (62.40)	6.25 (6.48)	3.47 (3.70)
38l	$(CH_2)_3$-CH_3	H	H	90	120—122	$C_{21}H_{25}NO_4S$	65.10 (65.29)	6.50 (6.83)	3.62 (3.39)
38m	CH_2COO-CH_2CH_3	H	H	85	132—134	$C_{21}H_{23}NO_6S$	60.42 (60.65)	5.55 (5.80)	3.36 (2.99)
38n	CH_3	NO_2	H	90	174—176	$C_{18}H_{18}N_2O_6S$	55.38 (55.09)	4.65 (4.51)	7.18 (7.35)
38o	CH_3	$N(CH_3)_2$	H	70	96—98	$C_{20}H_{24}N_2O_4S$	61.84 (61.55)	6.23 (6.40)	7.21 (7.11)
38p	CH_3	H	NO_2	94	175—177	$C_{18}H_{18}N_2O_6S$	55.37 (55.25)	4.65 (4.51)	7.18 (6.97)
38q	CH_3	Cl	H	93	156—158	$C_{18}H_{18}ClNO_4S$	56.92 (56.74)	4.78 (4.69)	3.69 (3.81)
38r	CH_3	CN	H	82	158—159	$C_{19}H_{18}N_2O_4S$	61.61 (61.77)	4.90 (5.17)	7.56 (7.32)
38t	CH_2Ph	$CONH_2$	H	63	149—151	$C_{25}H_{24}N_2O_5S$	64.65 (64.41)	5.21 (5.00)	6.03 (5.75)

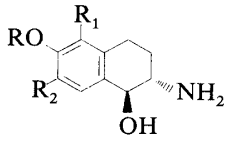
TABLE VIII. 2-Amino-3,4-dihydro-1(2*H*)-naphthalenones (**39**·HCl)



Compd. No.	R	R_1	R_2	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
39a	CH_2Ph	H	H	45	224—225	$C_{17}H_{17}NO_2 \cdot HCl$	67.21 (66.99)	5.97 (5.70)	4.61 (4.88)
39b	CH_2Ph-(*p*-Cl)	H	H	38	205	$C_{17}H_{16}ClNO_2 \cdot HCl$	60.36 (60.32)	5.07 (5.04)	4.14 (4.22)
39c	CH_2Ph-(*o*-Cl)	H	H	40	216—218	$C_{17}H_{16}ClNO_2 \cdot HCl$	60.36 (60.50)	5.07 (5.29)	4.14 (4.01)
39d	CH_2Ph (*m*-OCH_3)	H	H	23	175	$C_{18}H_{19}NO_3 \cdot HCl$	64.76 (64.81)	6.04 (6.03)	4.20 (4.21)
39e	$(CH_2)_2$-Ph	H	H	50	207—210	$C_{18}H_{19}NO_2 \cdot HCl$	68.02 (67.81)	6.34 (6.65)	4.41 (4.09)
39f	$(CH_2)_2$-cyclohexyl	H	H	—		[a]			
39h	CH_2CH_3	H	H	28	193—195	$C_{12}H_{15}NO_2 \cdot HCl$	59.62 (59.88)	6.67 (6.91)	5.80 (5.48)
39i	$CH(CH_3)_2$	H	H	24	205—207	$C_{13}H_{17}NO_2 \cdot HCl$	61.05 (61.01)	7.09 (7.22)	5.48 (5.35)
39j	$CH_2CH=CH_2$	H	H	47	195—198	$C_{13}H_{15}NO_2 \cdot HCl$	61.54 (61.41)	6.36 (6.17)	5.52 (5.30)
39k	$(CH_2)_2$-OCH_2CH_3	H	H	32	183—185	$C_{14}H_{19}NO_3 \cdot HCl$	58.84 (58.62)	7.06 (6.77)	4.90 (4.61)
39l	$(CH_2)_3$-CH_3	H	H	47	190—193	$C_{14}H_{19}NO_2 \cdot HCl$	62.33 (62.58)	7.47 (7.71)	5.19 (4.80)
39m	CH_2COO-CH_3 [b]	H	H	57	205—207	$C_{13}H_{15}NO_4 \cdot HCl$	54.65 (54.47)	5.65 (5.70)	4.90 (4.81)
39n	CH_3	NO_2	H	64	244—246	$C_{11}H_{12}N_2O_4 \cdot HCl$	48.45 (48.19)	4.81 (4.67)	10.27 (10.44)
39o	CH_3	$N(CH_3)_2$	H	—		[a]			
39p	CH_3	H	NO_2	34	195—198	$C_{11}H_{12}N_2O_4 \cdot HCl$	48.45 (48.08)	4.81 (5.06)	10.27 (10.15)
39q	CH_3	Cl	H	67	250—252	$C_{11}H_{12}ClNO_2 \cdot HCl$	50.40 (50.14)	5.00 (4.77)	5.34 (5.26)
39r	CH_3	CN	H	77	>300	$C_{12}H_{12}N_2O_2 \cdot HCl$	57.06 (56.56)	5.15 (5.29)	11.09 (10.79)
39t	CH_2Ph	$CONH_2$	H	48	227—230	$C_{18}H_{18}N_2O_3 \cdot HCl$	62.34 (62.60)	5.52 (5.71)	8.08 (7.73)

a) Used for the next step without purification.
b) Transesterification occurred on recrystallization from MeOH.

TABLE IX. *trans*-2-Amino-1,2,3,4-tetrahydronaphthalen-1-ols (**40**·HCl)



Compd. No.	R	R_1	R_2	Yield (%)	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (d_6-DMSO) C_1–H δJ [a]
40a	CH_2Ph	H	H	72	210—212	$C_{17}H_{19}NO_2\cdot HCl$	66.77 (66.51)	6.59 (6.69)	4.58 (4.59)	4.60 (9)
40b	CH_2Ph-(*p*-Cl)	H	H	29	177—178	$C_{17}H_{18}ClNO_2\cdot HCl$	60.01 (60.36)	5.63 (5.96)	4.12 (3.98)	4.60 (9)
40c	CH_2Ph-(*o*-Cl)	H	H	73	199—203	$C_{17}H_{18}ClNO_2\cdot HCl$	60.01 (60.25)	5.63 (5.63)	4.12 (4.14)	4.65 (9)
40d	CH_2Ph-(*m*-OCH_3)	H	H	59	182—185	$C_{18}H_{21}NO_3\cdot HCl$	64.37 (64.27)	6.60 (6.60)	4.17 (4.11)	4.62 (9)
40e	$(CH_2)_2$-Ph	H	H	52	196—197	$C_{18}H_{21}NO_2\cdot HCl$	67.59 (67.41)	6.93 (6.90)	4.38 (4.47)	4.65 (9)
40f	$(CH_2)_2$-cyclohexyl	H	H	19[b]	190—192	$C_{18}H_{27}NO_2\cdot HCl$	66.34 (66.15)	8.66 (8.46)	4.30 (4.37)	4.62 (9)
40g	CH_3	H	H	—	[c]					4.60 (9)
40h	CH_2CH_3	H	H	45	195—197	$C_{12}H_{17}NO_2\cdot HCl$	59.13 (58.99)	7.44 (7.09)	5.75 (5.66)	4.64 (9)
40i	$CH(CH_3)_2$	H	H	50	223—224	$C_{13}H_{19}NO_2\cdot HCl$	60.57 (60.52)	7.82 (7.85)	5.44 (5.44)	4.60 (8)
40j	$CH_2CH=CH_2$	H	H	57	205—206	$C_{13}H_{17}NO_2\cdot HCl$	61.05 (60.85)	7.09 (6.85)	5.48 (5.41)	4.62 (9)
40k	(CH_2)-OCH_2CH_3	H	H	39	180—182	$C_{14}H_{21}NO_3\cdot HCl$	58.42 (57.99)	7.71 (7.55)	4.87 (4.81)	4.63 (9)
40l	$(CH_2)_3$-CH_3	H	H	50	193—195	$C_{14}H_{21}NO_2\cdot HCl$	61.85 (61.81)	8.16 (8.00)	5.16 (5.16)	4.60 (9)
40m	CH_2COO-CH_3	H	H	57	178—179	$C_{13}H_{17}NO_4\cdot HCl$	54.26 (54.28)	6.30 (6.42)	4.87 (5.13)	4.60 (9)
40n	CH_3	NO_2	H	76	>300	$C_{11}H_{14}N_2O_4\cdot HCl$	48.09 (47.83)	5.50 (5.45)	10.20 (10.04)	4.72 (8)
40o	CH_3	$N(CH_3)_2$	H	13[b]	245—247	$C_{13}H_{20}N_2O_2\cdot HCl$	57.24 (57.03)	7.76 (7.51)	10.27 (10.08)	4.60 (9)
40p	CH_3	H	NO_2	60	>300	$C_{11}H_{14}N_2O_4\cdot HCl$	48.09 (47.80)	5.50 (5.38)	10.20 (10.11)	4.75 (9)
40q	CH_3	Cl	H	74	265—267	$C_{11}H_{14}ClNO_2\cdot HCl$	50.01 (49.72)	5.72 (5.79)	5.30 (5.40)	4.70 (9)
40r	CH_3	CN	H	91	275—277	$C_{11}H_{14}N_2O_2\cdot HCl$	54.43 (54.45)	6.23 (6.07)	11.55 (11.67)	4.70 (9)
40s	CH_2Ph	$COOCH_3$	H	—	[d]					
40t	CH_2Ph	$CONH_2$	H	66	220—222	$C_{18}H_{20}N_2O_3\cdot HCl$	61.98 (62.18)	6.07 (6.23)	8.03 (7.79)	4.65 (9)

a) Coupling constants *J* are expressed in Hz. *b*) Based on tosyloxime **38**. *c*) Reference 15. *d*) Reference 7.

HCl (2 g) in MeOH (50 ml) was treated portionwise with $NaBH_4$ (2 g) at room temperature. After being stirred for 30 min, the reaction mixture was diluted with water (300 ml) and extracted with $CHCl_3$ (50 ml × 3). The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in ether (50 ml) and 20% HCl–EtOH (5 ml) was added to the solution to deposit **40**·HCl, which was recrystallized from MeOH–ether to give colorless crystals.

***trans*-2-(*N*-Substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (10—31, Table I)**——General Procedure: $NaBH_3CN$ (1 g) was added portionwise to a stirred solution of **40**·HCl (1 g) and ketone (2—5 g) in MeOH (30 ml) at 5 °C. After standing overnight at room temperature, the reaction mixture was acidified with 10% HCl under cooling, diluted with excess water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$ (30 ml × 3). The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give a viscous oil. *N*-Substituted amino alcohol hydrochloride (**10—31**·HCl) was prepared by addition of ethanolic HCl to an ethereal solution of free base and recrystallized from MeOH–ether. Compound **10b** was led to the hydrogen oxalate by treatment with oxalic acid in EtOH followed by dilution with ether. A hydrogen fumarate drivative of compound **11** was obtained by treatment with a saturated solution of fumaric acid in ether.

***trans*-6-Hydroxy-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol (8, Table I)**——Free base of **10a** (1.3 g) prepared by neutralization of the hydrochloride with aqueous $NaHCO_3$ followed by extraction with AcOEt and evaporation was dissolved in MeOH (50 ml). The solution was subjected to catalytic hydrogenolysis over 10% Pd-C (1 g) at ambient temperature and pressure. After hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was treated with a solution of fumaric acid in ether to give **8a** hydrogen fumarate (0.6 g) as colorless crystals. ^{1}H-NMR (d_6-DMSO) δ: 1.30 (3H, CH_3), 1.80—2.40 (4H, m, CH_2 × 2), 2.55—2.90 (4H, m, CH_2 × 2), 3.20—3.60 (2H, m, CH × 2), 4.85 (1H, d, J = 9 Hz, CH–OH), 6.65 (1H, d, J = 2 Hz, phenyl proton), 6.72 (1H, dd, J = 8, 2 Hz, phenyl proton), 7.30—7.50 (6H, m, phenyl protons). In a similar manner **10b** hydrogen oxalate and **10c**·HCl were debenzylated to crystalline **8b** hydrogen fumarate and **8c**·HCl, respectively.

***trans*-1,6-Dihydroxy-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalene-5-carboxamide (9, Table I)**——A solution of **31a**·HCl (1 g) in MeOH (50 ml) was hydrogenated over 10% Pd-C (1 g) at room temperature under atmospheric pressure until 1 eq of hydrogen was consumed. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* and diluted with ether (50 ml) to give **9a**·HCl (0.56 g) as a colorless amorphous powder. ^{1}H-NMR (d_6-DMSO) δ: 1.33 (d, J = 6 Hz, 3H), 1.70—2.70 (m, 4H), 2.50—2.85 (m, 4H), 3.20—3.45 (m, 2H), 4.80 (d, J = 9 Hz, 1H), 7.00 (d, J = 6 Hz, 1H), 7.40—7.53 (m, 6H). Compound **9b**·HCl was prepared in a similar manner from **31b**·HCl.

***trans*-Methyl 1,6-Dihydroxy-2-(*N*-substituted amino)-1,2,3,4-tetrahydro-5-naphthoate (32, Table I)**——Compounds **30a**·HCl and **30b**·HCl were converted to **32a**·HCl and **32b**·HCl by catalytic hydrogenolysis in a manner similar to that described for the preparation of **9a**.

***trans*-5-Amino-6-methoxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydronaphthalen-1-ol (24a, Table I)**——A solution of **23a**·HCl (2 g) in MeOH (200 ml) was subjected to catalytic reduction over 10% Pd-C (1 g) at ambient temperature and pressure. After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. Aqueous $NaHCO_3$ (50 ml) was added to the residue, and the mixture was extracted with AcOEt (50 ml). The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give **24a** as a viscous oil, which was led to the fumarate (1 g) by treatment with a solution of fumaric acid in ether. In a similar manner **23b**·HCl and **26a**·HCl were hydrogenated to **24b** hydrogen fumarate and **27** fumarate, respectively.

***trans*-2-Benzhydrylamino-5-nitro-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (23c, Table I)**——A mixture of **40n** (2 g), CH_3CN (60 ml), benzhydryl chloride (4 g), Et_3N (2 g) and KI (1 g) was refluxed for 5 h with stirring. The mixture was concentrated *in vacuo*, then water (100 ml) was added to the residue and the resulting mixture was extracted with AcOEt (200 ml). The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give **23c** as an oil, which yielded colorless needles of the hydrochloride (2.4 g) upon treatment with 20% ethanolic HCl (5 ml) followed by dilution with ether.

***cis*-2-Amino-5-methoxyindan-1-ol (47b)**——1) A suspension of $LiAlH_4$ (3 g) was added dropwise to a solution of 2-hydroxyimino-5-methoxy-1-indanone[10] (**46b**, 2 g) in tetrahydrofuran (THF) (25 ml), and the mixture was refluxed for 7.5 h with stirring. The mixture was cooled, and water was added dropwise under ice-cooling to decompose excess $LiAlH_4$. AcOEt (100 ml) was added to the mixture and the inorganic precipitate was filtered off. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give **47b** as an oily residue, which was led to the hydrochloride (0.1 g), colorless crystals, mp 194 °C (dec.) (lit. mp 199 °C).[10] ^{1}H-NMR (d_6-DMSO) δ: 5.40 (1H, d, J = 5 Hz, CH–OH). 2) Compound **46b** (6.4 g) was reduced by catalytic hydrogenation in a manner similar to that described for the preparation of **44**. The product was led to the hydrochloride (5.5 g, 75%) which was identical with **47b** prepared above.

***cis*-2-Amino-5-benzyloxyindan-1-ol (47a)**——A mixture of **45b**[14] (15.6 g), $AlCl_3$ (25.6 g) and benzene (200 ml) was refluxed for 1 h with stirring. After cooling, the mixture was poured into ice-water (500 ml), and the resulting precipitate was collected by filtration and recrystallized from EtOH to give 5-hydroxy-1-indanone (12 g, 84%) as colorless crystals, which were dissolved in DMF (120 ml). Benzyl chloride (12.4 g), K_2CO_3 (6.7 g) and KI (1 g) were

added to the solution and the resulting mixture was heated at 100 °C for 2 h. After cooling, the mixture was poured into water (500 ml) and the resulting solid was recrystallized from EtOH to give 5-benzyloxy-1-indanone (**45a**, 15.3 g, 79%) as colorless prisms, mp 105.5—106 °C. A mixture of **45a** (15 g), MeOH (150 ml), conc. HCl (10 ml) and isoamylnitrite (15 ml) was warmed at 50 °C for 30 min. The deposited pale yellow needles were collected by filtration to give α-hydroxyimino ketone **46a** (11.8 g, 70%), mp 202—205 °C. *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.90; N, 5.24. Found: C, 71.92; H, 4.86; N, 4.96. Compound **46a** (10.2 g) was reduced to **47a** with $LiAlH_4$ (10.2 g) in a manner similar to that described for the preparation of **47b**. Compound **47a** was led to the hydrochloride (3.65 g, 33%), colorless prisms, mp 208—210 °C (dec.). *Anal.* Calcd for $C_{16}H_{17}NO_2 \cdot HCl$: C, 65.86; H, 6.22; N, 4.80. Found: C, 66.07; H, 6.21; N, 4.80. ^{1}H-NMR (d_6-DMSO) δ: 5.66 (1H, d, J=5 Hz, C<u>H</u>–OH).

***cis*-5-Alkoxy-2-(*N*-substituted amino)indan-1-ol (33b—e, Table II)**——Compounds **47a**·HCl and **47b**·HCl were alkylated to **33b**—**e** with acetone or benzyl acetone in the presence of $NaBH_3CN$ in a manner similar to that described for the preparation of **10**. Compounds **33b** fumarate, **33c**·HCl, **33d**·HCl and **33e**·HCl were obtained as colorless crystals.

***cis*-5-Hydroxy-2-(1-methyl-3-phenylpropyl)aminoindan-1-ol (33a, Table II)**——Catalytic hydrogenolysis of **33b** was carried out by a procedure similar to that described for the preparation of **8a** to give **33a** fumarate as colorless crystals.

***cis*-6-Amino-2-butoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (48b)**——2-Hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[11] (14 g) was allowed to react in DMF (100 ml) with butyl bromide (13 g) in the presence of K_2CO_3 (6.6 g) and KI (3 g) as described for the preparation of **36b**—**l**. 2-Butoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (17 g, 99%) was obtained as a viscous oil. A mixture of this ketone (17 g), isoamyl nitrite (50 g), 20% ethanolic HCl (32 ml) and ether (400 ml) was allowed to stand overnight at room temperature. Precipitated colorless crystals were collected by filtration to give 2-butoxy-6-hydroxyimino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (7 g, 36%) as colorless needles. $LiAlH_4$ (8 g) was added portionwise to a solution of this α-hydroxyimino ketone (6.5 g) in THF (200 ml) and the mixture was refluxed for 5 h with stirring, then cooled. Water was added dropwise under ice-cooling to decompose excess $LiAlH_4$. AcOEt (200 ml) was added to the mixture and the precipitate was filtered off. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo* to give **48b** as a colorless liquid, which was led to the hydrochloride (4 g, 57%), colorless crystals, mp 200—202 °C. *Anal.* Calcd for $C_{15}H_{23}NO_2 \cdot HCl$: C, 63.04; H, 8.46; N, 4.90. Found: C, 62.91; H, 8.70; N, 4.73. NMR (d_6-DMSO) δ: 4.65 (d, J= 2 Hz, 1H, C<u>H</u>–OH).

***cis* and *trans*-2-Alkoxy-6-(*N*-substituted amino)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (34b—e and 35b, c, Table III)**——Amino alcohols **48a**,[11] **48b** and **49** were alkylated with acetone or benzylacetone in the presence of $NaBH_3CN$ in a manner similar to that described for the preparation of **10** to give *N*-isopropylamino compounds (**34c**·HCl, **34e**·HCl and **35c** hydrogen fumarate) or *N*-(1-methyl-3-phenylpropyl)amino compounds (**34b** fumarate, **34d** fumarate and **35b** fumarate), respectively.

***cis* and *trans*-2-Hydroxy-6-(1-methyl-3-phenylpropyl)amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (34a and 35a, Table III)**——Compounds **34b** and **35b** were subjected to catalytic hydrogenolysis in a manner similar to that described for the preparation of **8a** to give **34a** fumarate and **35a** fumarate, respectively, as colorless needles.

***trans*-6-Amino-2-benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (49)**——Ac_2O (50 ml) was added dropwise to a stirred solution of **48a**[11] (10 g) in MeOH (200 ml) at room temperature. When the addition was complete, stirring was continued for 3 h then the reaction mixture was concentrated *in vacuo*. The residue was crystallized from ether–petroleum ether to give *cis*-6-acetylamino-2-benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (7 g, 61%) as colorless prisms, mp 90—92 °C. *Anal.* Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.56; H, 6.95; N, 4.39. CrO_3–H_2SO_4 (Jones reagent) was added dropwise to a stirred solution of the *cis*-acetylamino alcohol (7 g) in acetone (100 ml) at room temperature until the orange color of the reagent remained. Excess reagent was consumed by addition of MeOH, then the mixture was poured into water (300 ml) and extracted with AcOEt (200 ml). The extract was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from petroleum ether to give 6-acetylamino-2-benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (6 g, 86%) as colorless crystals, mp 130—132 °C. *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.00; H, 6.37; N, 4.21. $NaBH_4$ (3 g) was added portionwise to a stirred solution of the α-acetylamino ketone (6 g) in MeOH (100 ml) at room temperature. The reaction mixture was stirred for a further 1 h, then water (500 ml) was added and the whole was extracted with AcOEt (200 ml). The extract was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was crystallized from ether to give *trans*-6-acetylamino-2-benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (6 g, 99%) as colorless prisms, mp 148—150 °C. *Anal.* Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.68; H, 7.05; N, 4.22. A mixture of this *trans*-acetylamino alcohol (6 g), EtOH (50 ml) and 3 N NaOH (50 ml) was refluxed for 4 h with stirring. After cooling, the mixture was diluted with water (100 ml) and extracted with AcOEt (200 ml). The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in ether (200 ml) followed by addition of 20% ethanolic HCl (10 ml) to give **49**·HCl (4 g, 68%) as colorless needles, mp 176—178 °C. *Anal.* Calcd for $C_{18}H_{21}NO_2 \cdot HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.45; H. 6.68; N, 4.43. ^{1}H-NMR (d_6-DMSO) δ: 4.70 (1H, d, J=10 Hz, C<u>H</u>–OH).

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References and Notes

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12) All melting points were determined on a micro hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer. NMR spectra were recorded on a Varian T-60, HA-100 or EM-390 machine with Me_4Si as a standard.
13) *p*-Chlorobenzyl chloride, *o*-chlorobenzyl chloride, *m*-methoxybenzyl chloride, phenethyl bromide, cyclohexylethyl bromide, ethyl bromide, isopropyl bromide, allyl bromide, ethoxyethyl bromide, butyl iodide and ethyl bromoacetate were used. In the cases of phenethyl, cyclohexylethyl, ethyl, isopropyl and ethoxyethyl bromide, KI (1 g) was added to the reaction mixture.
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