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Synthesis and β-Adrenergic Blocking Activity of 2-(*N*-Substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol Derivatives

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In a search for a new structural type of β-adrenergic antagonist, a series of *trans*-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol derivatives (**3**—**36**) was synthesized in several steps from 3,4-dihydro-1(2*H*)-naphthalenone (**37**) having a variety of substituents at the 5-, 6-, 7- and 8-positions. Compounds **3**—**36** were tested *in vitro* for β-adrenergic activity. Among them, 2-benzhydrylamino-6-chloro-1,2,3,4-tetrahydronaphthalen-1-ol (**28c**) was found to show a fairly potent β-adrenergic blocking activity.

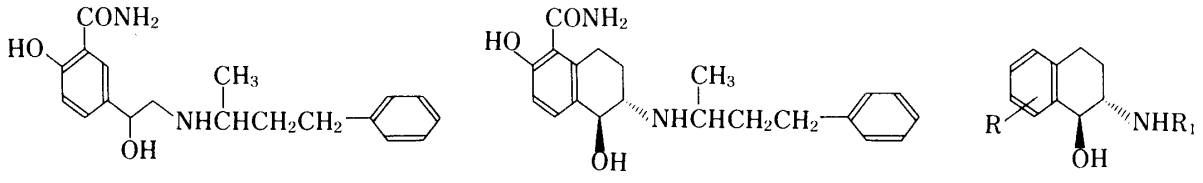
Keywords——β-adrenergic blocker; β-adrenergic activity; phenylethanolamine derivative; conformationally restricted analog; 2-amino-1,2,3,4-tetrahydronaphthalen-1-ol; Neber rearrangement

In the preceding paper, we reported the synthesis of *trans*-1,6-dihydroxy-2-(1-methyl-3-phenylpropyl)amino-1,2,3,4-tetrahydronaphthalene-5-carboxamide (**2**),[1] which is a conformationally restricted analog of labetalol (**1**).[2] Compound **2** was found to show a potent β-adrenergic blocking activity, but unlike **1**, it also possessed intrinsic β-stimulating activity, effecting an increase of beating rate in the rat. Assuming that this β-agonistic property of **2** might be inherent to the 6-hydroxytetrahydronaphthalene skeleton, we undertook to synthesize a wide variety of 2-aminotetrahydronaphthalen-1-ol derivatives without the 6-hydroxyl group, expecting to obtain a new type of β-adrenergic blocking agent.

In this paper, we report the synthesis and the biological activity of 2-amino-1,2,3,4,-tetrahydronaphthalen-1-ol derivatives (**3**—**36**, Table I) substituted with a variety of functional groups including alkoxy, aryloxy, alkoxycarbonyl, substituted amino, aryl, alkyl, halo, nitro, alkylthio and cyano groups at the 5-, 6-, 7-, and 8-positions of the naphthalene ring.

Chemistry

The synthesis of the *trans*-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ol derivatives (**3**—**36**) listed in Table I was performed according to the scheme shown in Charts 1—3. In the general procedure, excluding the 5,8-dimethoxy and 6-morpholino derivatives (**37i**, **37s**), a substituted 3,4-dihydro-1(2*H*)-naphthalenone derivative (**37**) was led to the



1 **2** **3—36**

Fig. 1

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tosyloxime (**39**) *via* the oxime (**38**), and **39** was subjected to the Neber rearrangement to give the α-amino ketone hydrochloride (**40**·HCl). In the case of the 5,8-dimethoxy derivative, the α-nitro ketone (**69**), prepared from **37i** according to Barfknecht's method,[3] was led to the α-acetamido ketone (**70**) by catalytic reduction over Raney nickel in a mixture of acetic acid and acetic anhydride. Hydrolysis of **70** with dilute hydrochloric acid afforded the α-amino ketone hydrochloride (**40i**·HCl). Since attempted conversion of 6-morpholino-3,4-dihydro-1(2*H*)-naphthalenone (**37s**) to the corresponding α-amino ketone (**40s**) by the above two routes proved to be unsuccessful, probably owing to the basicity of the morpholino group, compound **40s** was prepared by the following alternative route. Thus, **37s** was allowed to react with ethyl formate–sodium ethoxide and the resulting α-formyl ketone (**71**) was treated with sodium nitrite to give the α-hydroxyimino ketone (**72**). Compound **72** was hydrogenated over palladium-charcoal in the presence of hydrogen chloride to afford the 6-morpholino α-amino ketone hydrochloride (**40s**·HCl).

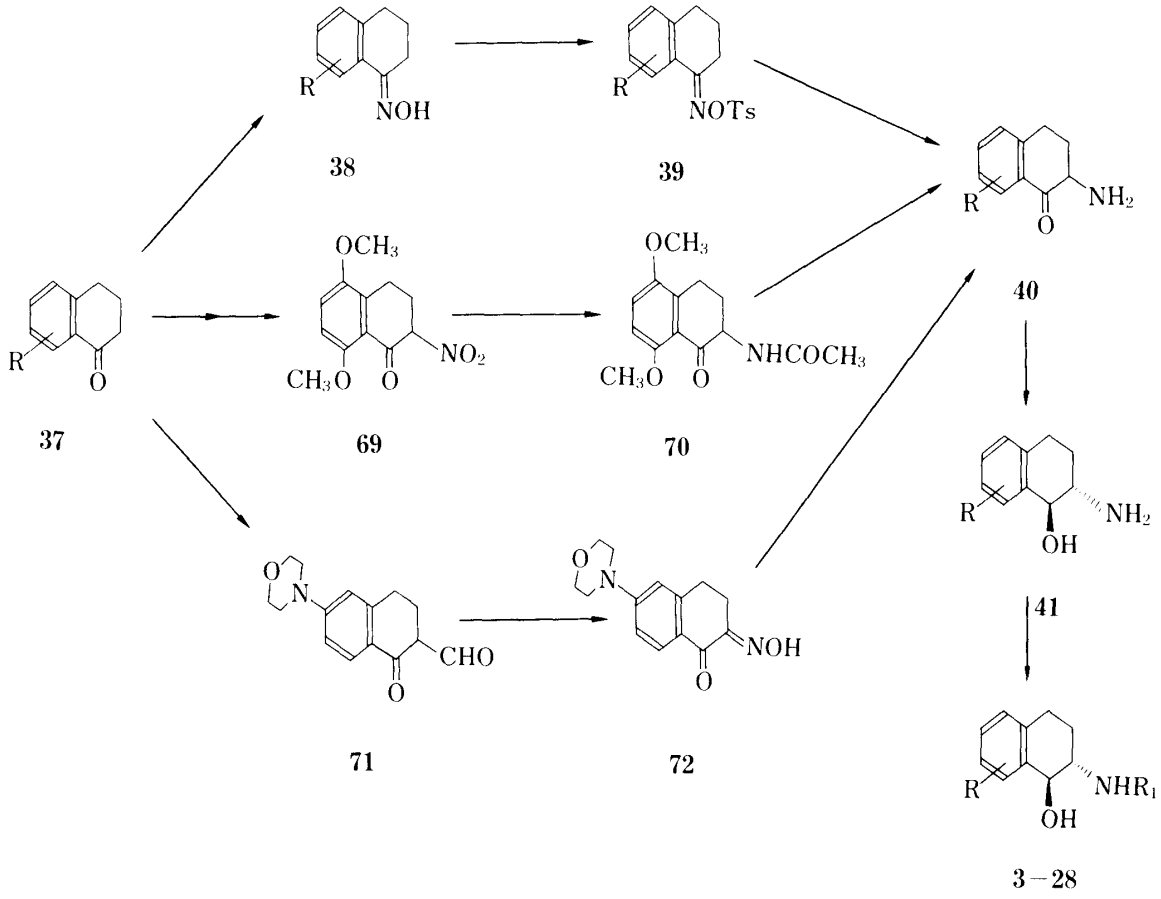

Chart 1

Reduction of **40**·HCl with sodium borohydride yielded *trans*-2-amino-1,2,3,4-tetrahydronaphthalen-1-ol derivatives (**41**, Table VI). The synthesis of *N*-substituted amino alcohol derivatives (**3**—**28**) was accomplished by the reductive alkylation of **41** with acetone or benzylacetone in the presence of sodium cyanoborohydride ($NaBH_3CN$). The *trans*-configuration of the amino alcohols was confirmed by the proton nuclear magnetic resonance (^{1}H-NMR) spectra which showed C_1–H as a doublet with a coupling constant (*J*) of 5—8 Hz (Tables I and VI).

Biological tests of the above series of 2-isopropylamino and 2-(1-methyl-3-phenylpropyl)amino alcohols revealed that the 6-chloro (**28a**, **28b**) and 6-butylthio (**23a**, **23b**) deriv-

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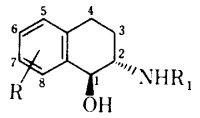
TABLE I. *trans*-2-(*N*-Substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (**3**—**36**)



Compd. No.	R	R^1	Yield (%)	Form	mp (°C) dec.	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (DMSO-d_6) C_1–H δ (J)[a]
3	5-$OCH_2CH=CH_2$	$CH(CH_3)_2$	59	HCl	195—197	$C_{16}H_{23}NO_2\cdot$ HCl	64.52 (64.51	8.12 8.14	4.70 4.56)	4.9 (7)
4	5-$O(CH_2)_3CH_3$	$CH(CH_3)_2$	78	HCl	194—196	$C_{17}H_{27}NO_2\cdot$ HCl	65.05 (64.74	8.99 9.32	4.46 4.74)	4.8 (6.5)
5	5-OCH_2Ph	$CH(CH_3)_2$	72	HCl	220—223	$C_{20}H_{25}NO_2\cdot$ HCl	69.05 (68.87	7.53 7.35	4.03 4.09)	4.8 (7)
6	5-OPh	$CH(CH_3)_2$	87	HCl	205—209	$C_{19}H_{23}NO_2\cdot$ HCl	68.35 (68.11	7.25 7.16	4.20 3.93)	4.8 (7.5)
7	5-$COOC_2H_5$	$CH(CH_3)_2$	48	HCl	193—195	$C_{16}H_{23}NO_3\cdot$ HCl	61.23 (61.07	7.71 7.76	4.46 4.58)	4.6 (7)
8	5-Ph	$CH(CH_3)_2$	85	HCl	265—267	$C_{19}H_{23}NO\cdot$ HCl	71.79 (71.54	7.71 7.71	4.41 4.41)	4.9 (8)
9	5-$N(CH_3)COOC_2H_5$	$CH(CH_3)_2$	57	HCl	130—131	$C_{17}H_{26}N_2O_3\cdot$ HCl	59.55 (59.61	7.94 7.80	8.17 8.21)	4.9 (8)
10a	5-Cl	$CH(CH_3)_2$	83	HCl	239—240	$C_{13}H_{18}ClNO\cdot$ HCl	56.53 (56.29	6.90 7.00	5.07 4.99)	4.6 (7)
10b	5-Cl	$CH(CH_3)CH_2CH_2Ph$	65	HCl	179—180	$C_{20}H_{24}ClNO\cdot$ HCl	65.57 (65.29	6.88 6.87	3.82 3.70)	4.8 (7.5)
11	5-OCH_3 8-OCH_3	$CH(CH_3)_2$	73	Fumarate	170—175	$C_{15}H_{23}NO_3\cdot$ $C_4H_4O_4$	59.83 (59.40	7.14 7.10	3.67 3.67)	5.0 (5)

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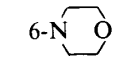
12a	5-CH_3 7-CH_3	$CH(CH_3)_2$	67	HCl	240—250	$C_{15}H_{23}NO\cdot$ HCl	66.77 (66.50	8.97 8.79	5.19 5.15)	4.8 (7.5)
12b	5-CH_3 7-CH_3	CH_3 | $CHCH_2CH_2Ph$	85	HCl	154—158	$C_{22}H_{29}NO\cdot HCl\cdot H_2O$	69.91 (69.48	8.53 8.30	3.71 4.14)	4.8 (8)
13a	5-CH_3 6-NO_2 7-CH_3	$CH(CH_3)_2$	90	HCl	>270	$C_{15}H_{22}N_2O_3\cdot$ HCl	57.23 (57.03	7.36 7.36	8.96 8.69)	5.0 (7)
13b	5-CH_3 6-NO_2 7-CH_3	CH_3 | $CHCH_2CH_2Ph$	91	HCl	210	$C_{22}H_{28}N_2O_3\cdot$ HCl	65.25 (64.84	7.22 7.21	6.92 6.84)	5.0 (7)
14a	5-OCH_3 6-$CH_2CH=CH_2$	$CH(CH_3)_2$	72	HCl	172—175	$C_{17}H_{25}NO_2\cdot$ HCl	65.47 (65.51	8.40 8.53	4.49 4.40)	4.8 (8)
14b	5-OCH_3 6-$CH_2CH=CH_2$	CH_3 | $CHCH_2CH_2Ph$	79	HCl	160—190	$C_{24}H_{31}NO_2\cdot HCl\cdot 1/2H_2O$	70.13 (70.05	8.09 7.96	3.41 3.90)	4.8 (8)
15	5-$O(CH_2)_3CH_3$ 6-$CH=CHCH_3$	$CH(CH_3)_2$	98	HCl	174—177	$C_{20}H_{31}NO_2\cdot$ HCl	67.87 (67.58	9.11 9.17	3.96 4.06)	4.7 (7)
16	5-OCH_2Ph 6-$CH=CHCH_3$	CH_3 | $CHCH_2CH_2Ph$	94	Fumarate	135—140	$C_{30}H_{35}NO_2\cdot 1/2C_4H_4O_4\cdot 1/2H_2O$	75.56 (75.66	7.53 7.42	2.75 3.10)	4.5 (7)
17	5,6-O–$\overset{CH_3}{\underset{}{C}}HCH_2$–	$CH(CH_3)_2$	86	HCl	220—240	$C_{16}H_{23}NO_2\cdot$ HCl	64.53 (64.17	8.12 8.42	4.70 4.58)	4.7 (7)
18	5,6-N=$\overset{Ph}{\underset{}{C}}$–O–	$CH(CH_3)_2$	82	HCl	273—274	$C_{20}H_{22}N_2O_2\cdot HCl\cdot 2H_2O$	60.83 (60.53	6.89 6.60	7.10 6.94)	5.0 (7)
19	6-N$\overset{CH_3}{\underset{COOC_2H_5}{}}$	$CH(CH_3)_2$	75	HCl	218—220	$C_{17}H_{26}N_2O_3\cdot$ HCl	59.55 (59.38	7.94 7.96	8.17 8.19)	4.8 (7)
20	6-N$\overset{CH_3}{\underset{COPh}{}}$	$CH(CH_3)_2$	91	HCl	229—230	$C_{21}H_{26}N_2O_2\cdot$ HCl	67.26 (67.21	7.26 7.38	7.47 7.33)	4.7 (7.5)
21	6- 	$CH(CH_3)_2$	27	HCl	195—200	$C_{17}H_{26}N_2O_2\cdot 2HCl\cdot 3/2H_2O$	52.31 (51.93	8.01 7.58	7.18 7.10)	4.8 (7)
22a	6-OPh	$CH(CH_3)_2$	68	HCl	219—220	$C_{19}H_{23}NO_2\cdot$ HCl	68.35 (68.41	7.25 7.03	4.20 4.11)	4.7 (8)

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TABLE I. continued

Compd. No.	R	R^1	Yield (%)	Form	mp (°C) dec.	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (DMSO-d_6) C_1–H δ (J)[a]
22b	6-OPh	CH_3 $CHCH_2CH_2Ph$	37	HCl	192—194	$C_{26}H_{29}NO_2 \cdot$ HCl	73.65 (73.44	7.13 7.20	3.30 3.27)	4.6 (8)
23a	6-$S(CH_2)_3CH_3$	$CH(CH_3)_2$	70	HCl	185—186	$C_{17}H_{27}NOS \cdot$ HCl	61.90 (61.61	8.56 8.54	4.25 4.21)	4.8 (7)
23b	6-$S(CH_2)_3CH_3$	CH_3 $CHCH_2CH_2Ph$	80	HCl	155—157	$C_{24}H_{33}NOS \cdot$ HCl	68.63 (68.50	8.16 7.91	3.34 3.49)	4.9 (8)
23c	6-$S(CH_2)_3CH_3$	$CH(Ph)_2$	25	HCl	205—207	$C_{27}H_{31}NOS \cdot$ HCl	71.43 (71.20	7.11 7.07	3.09 3.13)	4.8 (7)
24	6-CN	$CH(CH_3)_2$	88	HCl	197—198	$C_{14}H_{18}N_2O \cdot$ HCl	63.02 (63.05	7.18 7.11	10.50 10.50)	4.8 (8)
25	6-$COOC_2H_5$	$CH(CH_3)_2$	86	HCl	225—228	$C_{16}H_{23}NO_3 \cdot$ HCl	61.23 (60.85	7.71 7.71	4.46 4.26)	4.9 (7)
26	6-Ph	$CH(CH_3)_2$	70	HCl	263—264	$C_{19}H_{23}NO \cdot$ HCl	70.92 (71.13	7.61 7.70	4.60 4.42)	4.8 (7)
27a	6-Br	$CH(CH_3)_2$	87	HCl	250—252	$C_{13}H_{18}BrNO \cdot$ HCl	48.69 (48.66	5.97 5.99	4.37 4.65)	4.8 (7)
27b	6-Br	CH_3 $CHCH_2CH_2Ph$	89	HCl	202—204	$C_{20}H_{24}BrNO \cdot$ HCl	58.47 (58.48	6.13 5.94	3.41 3.41)	4.8 (7)
28a	6-Cl	$CH(CH_3)_2$	65	HCl	225—227	$C_{13}H_{18}ClNO \cdot$ HCl	56.52 (56.53	6.93 7.05	5.07 4.91)	4.9 (8)
28b	6-Cl	CH_3 $CHCH_2CH_2Ph$	82	HCl	195—196	$C_{20}H_{24}ClNO \cdot$ HCl	65.57 (65.41	6.88 6.90	3.82 3.83)	4.9 (7)
28c	6-Cl	$CH(Ph)_2$	42	HCl	232—234	$C_{23}H_{22}ClNO \cdot$ HCl	69.00 (68.87	5.79 5.70	3.50 3.37)	4.7 (7)

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28d	6-Cl	$\begin{matrix}CH_3\\ \vert\\ CHCH_2Ph\end{matrix}$	81	HCl	224—226	$C_{19}H_{22}ClNO\cdot$ HCl	64.77 (64.69	6.58 6.60	3.98 3.97)	4.6 (8)
28e	6-Cl		82	HCl	255—256	$C_{16}H_{21}ClNO\cdot$ HCl	60.76 (60.83	7.33 7.39	4.43 4.55)	4.6 (8)
29	5-CH_2OH	$CH(CH_3)_2$	64	Fumarate	242—244	$C_{14}H_{21}NO_2\cdot$ $1/2C_4H_4O_4$	65.51 (65.24	7.90 7.91	4.78 4.87)	4.8 (7)
30	5-$N(CH_3)_2$	$CH(CH_3)_2$	47	Fumarate	190—191	$C_{15}H_{24}N_2O\cdot$ $C_4H_4O_4$	62.62 (62.50	7.74 7.74	7.69 7.53)	4.8 (7)
31a	5-CH_3 6-NH_2 7-CH_3	$CH(CH_3)_2$	71	HCl	191—193	$C_{15}H_{24}N_2O\cdot$ $HCl\cdot 1/2H_2O$	61.32 (61.65	9.20 9.16	9.54 9.30)	—
31b	5-CH_3 6-NH_2 7-CH_3	$\begin{matrix}CH_3\\ \vert\\ CHCH_2CH_2Ph\end{matrix}$	50	HCl	145—150	$C_{22}H_{30}N_2O\cdot$ $HCl\cdot H_2O$	67.24 (67.33	8.46 7.83	7.13 7.13)	4.8 (6)
32	5-OCH_3 6-$(CH_2)_2CH_3$	$\begin{matrix}CH_3\\ \vert\\ CHCH_2CH_2Ph\end{matrix}$	73	HCl	170—182	$C_{24}H_{33}NO_2\cdot$ $HCl\cdot H_2O$	68.30 (68.41	8.60 8.30	3.32 3.75)	4.8 (7)
33	5-$O(CH_2)_3CH_3$ 6-$(CH_2)_2CH_3$	$CH(CH_3)_2$	81	HCl	185—189	$C_{20}H_{33}NO_2\cdot$ HCl	67.49 (66.99	9.63 9.70	3.94 3.85)	4.8 (7)
34	5-OH 6-$(CH_2)_2CH_3$	$\begin{matrix}CH_3\\ \vert\\ CHCH_2CH_2Ph\end{matrix}$	63	Fumarate	185	$C_{23}H_{31}NO_2\cdot$ $C_4H_4O_4$	69.06 (68.94	7.51 7.59	2.98 2.83)	4.7 (7)
35	6-$N(CH_3)_2$	$CH(CH_3)_2$	79	HCl	218—220	$C_{15}H_{24}N_2O\cdot$ 2HCl	56.07 (56.05	8.16 8.20	8.72 8.61)	4.6 (7)
36	6-CH_2OH	$CH(CH_3)_2$	63	Fumarate	201—202	$C_{14}H_{21}NO_2\cdot$ $1/2C_4H_4O_4\cdot H_2O$	61.71 (61.94	8.09 8.14	4.50 4.24)	4.7 (7)

a) Expressed in Hz.

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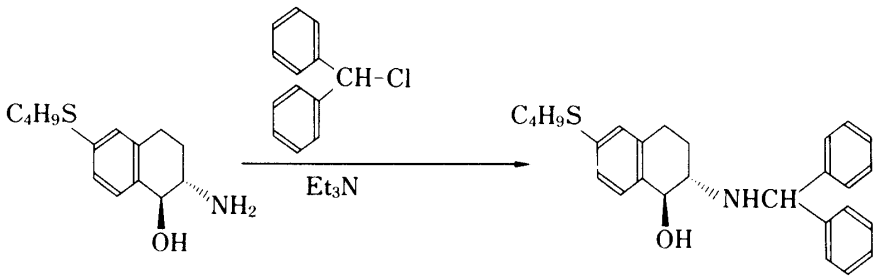
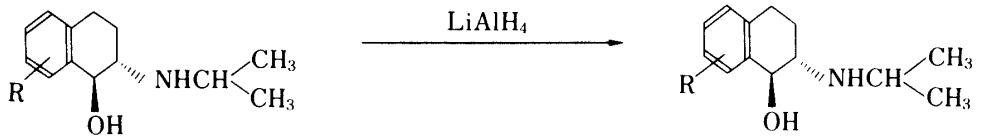
atives possessed β-adrenergic blocking activity. Therefore, several related *N*-alkylated derivatives of the 6-chloro and 6-butylthio amino alcohols were further prepared. The 2-benzhydrylamino (**28c**), 2-(1-methyl-2-phenylethyl)amino (**28d**) and 2-cyclohexylamino (**28e**) derivatives of 6-chloro-1,2,3,4-tetrahydronaphthalen-1-ol were obtained by the reaction of **41z** (**41**: R=6-Cl) with the corresponding ketone and $NaBH_3CN$. Since reductive alkylation of **41u** (**41**: R=6-SC_4H_9) with benzophenone was unsuccessful, direct alkylation using benzhydryl chloride[1] was applied for the synthesis of **23c**.

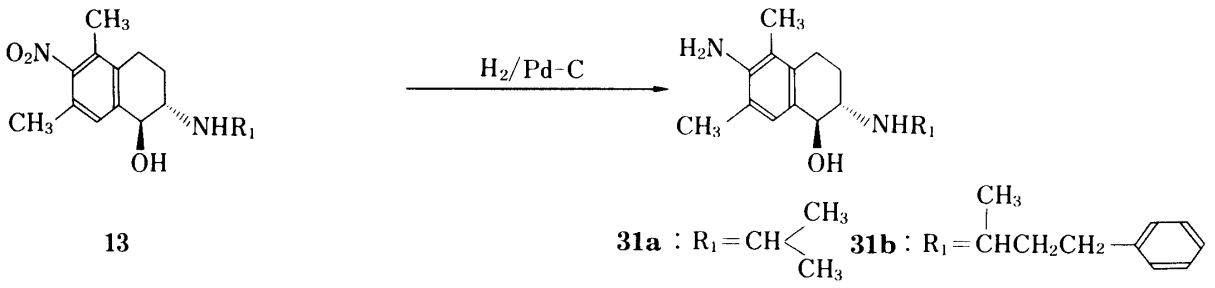


41u **23c**

Chart 2



7 : R=5-$COOC_2H_5$, **9** : R=5-$N(CH_3)COOC_2H_5$, **29** : R=5-CH_2OH, **30** : R=5-$N(CH_3)_2$
19 : R=6-$N(CH_3)COOC_2H_5$, **25** : R=6-$COOC_2H_5$, **35** : R=6-$N(CH_3)_2$, **36** : R=6-CH_2OH



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31a : R_1=$CH(CH_3)_2$ **31b** : R_1=$CH(CH_3)CH_2CH_2$-Ph

14b : R=OCH_3, R_1=$CH(CH_3)CH_2CH_2$-Ph
15 : R=$O(CH_2)_3CH_3$, R_1=$CH(CH_3)_2$
16 : R=OCH_2-Ph, R_1=$CH(CH_3)CH_2CH_2$-Ph

32 : R=OCH_3, R_1=$CH(CH_3)CH_2CH_2$-Ph
33 : R=$O(CH_2)_3CH_3$, R_1=$CH(CH_3)_2$
34 : R=OH, R_1=$CH(CH_3)CH_2CH_2$-Ph

Chart 3

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Compounds **7**, **9**, **13**, **14**, **15**, **16**, **19**, and **25** having a functional group convertible to another functional group by reduction, were led to the corresponding derivatives by treatment with lithium aluminum hydride ($LiAlH_4$) or by catalytic hydrogenation (Chart 3). Thus, the carbamates (**9**, **19**) and esters (**7**, **25**) were respectively converted to 5- or 6-(*N*,*N*-dimethylamino)-(**30**, **35**) and 5- or 6-hydroxymethyl-(**29**, **36**) amino-1,2,3,4-tetrahydronaphthalen-1-ol by treatment with $LiAlH_4$. Compounds containing a nitro or vinyl group (**13a**, **13b**, **14b** and **15**) were converted to the corresponding amino (**31a** and **31b**) and alkyl (**32** and **33**) derivatives by catalytic hydrogenation over palladium-charcoal. In the case of **16**, catalytic hydrogenolysis of the *O*-benzyl group and hydrogenation of the vinyl group occurred simultaneously to afford a phenol derivative (**34**).

The key intermediates for the above synthesis, 3,4-dihydro-1(2*H*)-naphthalenone (designated as tetralone) derivatives (**37**), were prepared by a variety of methods as described below.

5-Substituted Tetralones (37a—f)

5-Allyloxy-(**37a**),[4] 5-butoxy-(**37b**), 5-benzyloxy-(**37c**) and 5-phenoxy-(**37d**) tetralones were obtained by the reaction of 5-hydroxytetralone (**42**)[5] with the corresponding halides. 5-Ethoxycarbonyltetralone (**37e**) was obtained according to the literature.[6] 5-Phenyltetralone (**37f**) was prepared from 2-phenylaniline (**43**) *via* the sequence of steps depicted in Chart 4. Thus, **43** was converted to the corresponding bromide (**44**) by means of the Sandmeyer reaction. The Grignard reaction of **44** with *N*-methylformanilide followed by hydrolysis of the resulting intermediate gave 2-phenylbenzaldehyde (**45**), which was led to its homolog **47** by means of the Darzen condensation with subsequent decarboxylation of the resulting glycidic acid derivative **46**. The Wittig reaction of **47** with ethoxycarbonylmethylene triphenylphos-

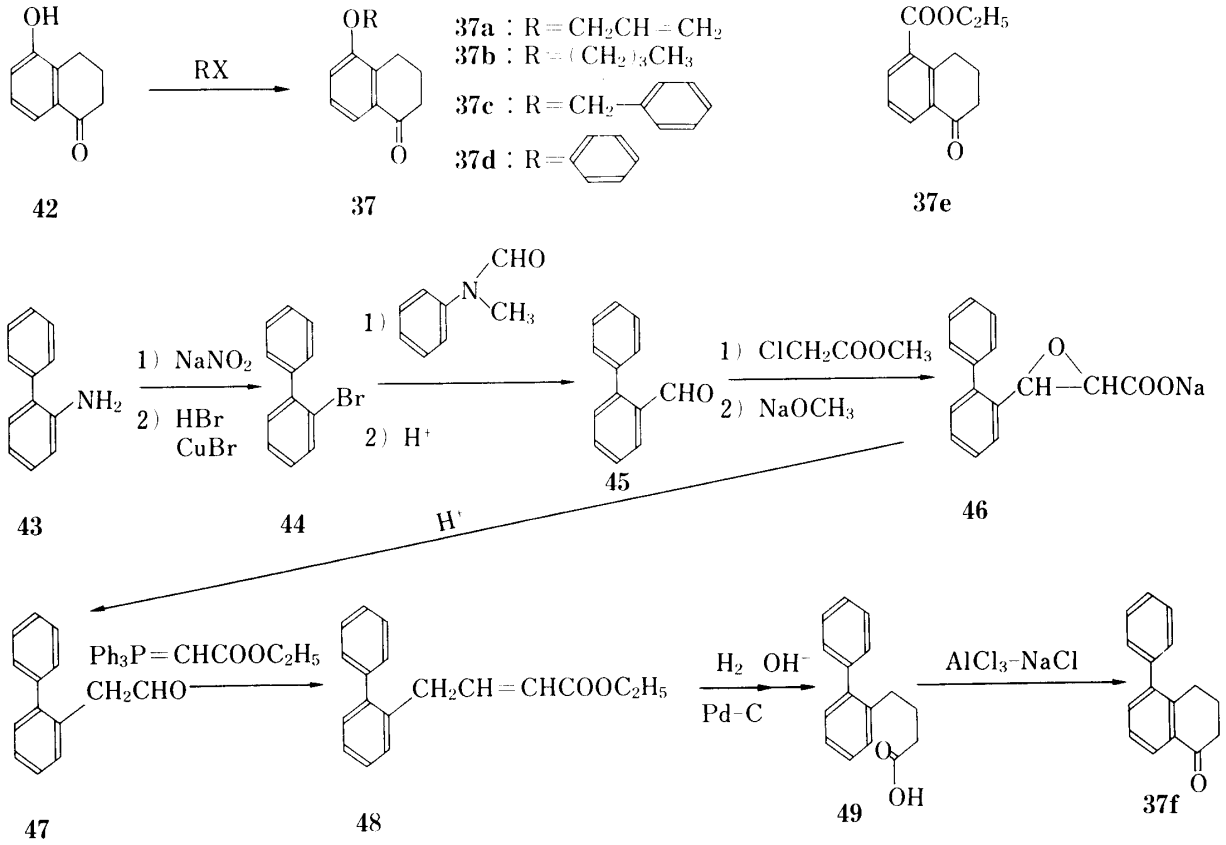

Chart 4

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phorane, affording ethyl 4-(2-biphenylyl)-2-butenoate (**48**), followed by catalytic hydrogenation and hydrolysis yielded the butanoic acid (**49**). Treatment of **49** with a mixture of NaCl and $AlCl_3$[7] effected cyclization to **37f**.

5-Amino- and 5-chlorotetralones (**55** and **37h**) were synthesized from 6-hydroxy-5-nitrotetralone (**51**)[8] by the routes shown in Chart 5. Thus, **51** was led to the thiocarbamate (**52**) by reaction with dimethylaminothiocarbonyl chloride, which in turn was thermally rearranged to the *N*,*N*-dimethylcarbamoyl derivative (**53**). Alkaline hydrolysis of **53** gave 6-mercapto-5-nitrotetralone (**54**). Desulfurization of **54** with Raney nickel yielded 5-amino-tetralone (**55**) by the simultaneous reduction of the nitro group. Compound **55** was led to the *N*-ethoxycarbonyl-*N*-methyl congener (**37g**) by N-protection with the trifluoroacetyl group, methylation with methyl iodide, and alkaline hydrolysis. On the other hand, the Sandmeyer reaction of **55** afforded 5-chlorotetralone (**37h**).

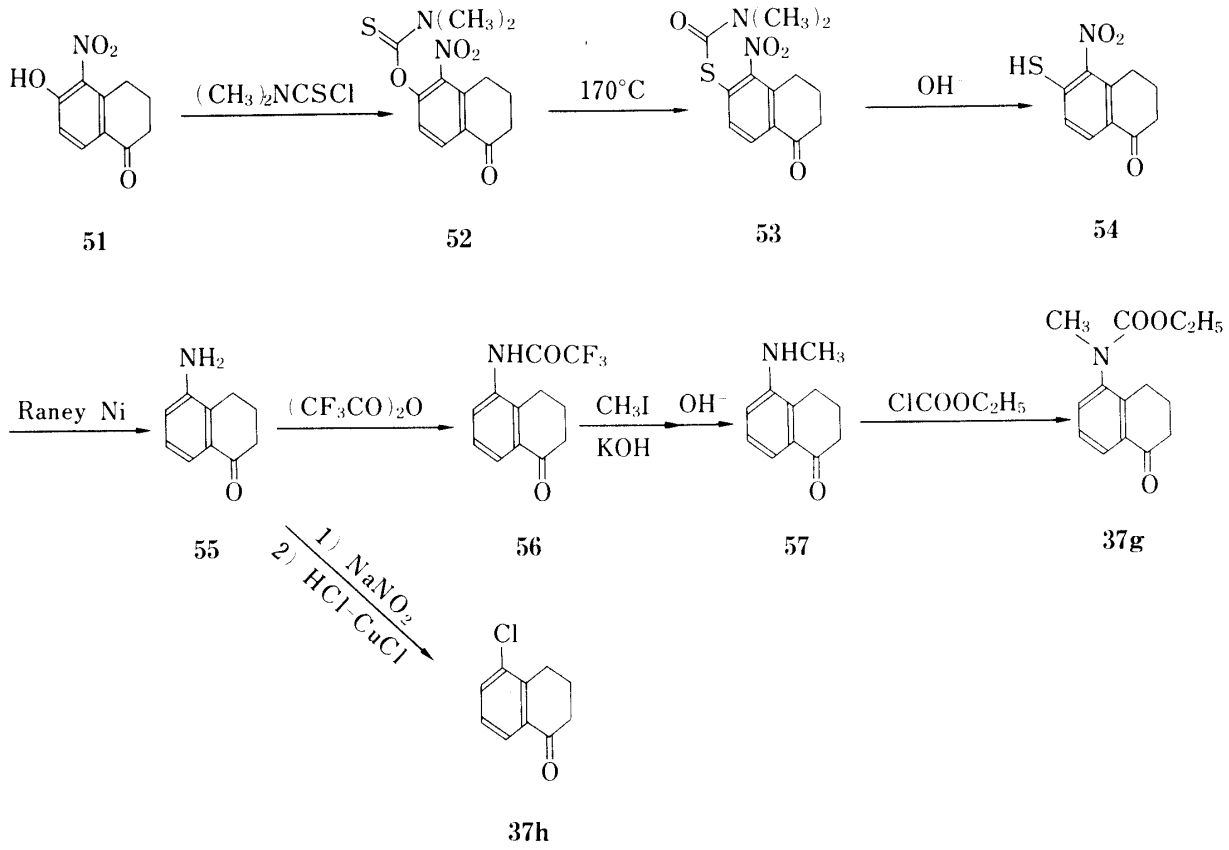

Chart 5

Di- and Trisubstituted Tetralones (37i—37p)

5,8-Dimethoxy-,[9] 5,7-dimethyl,[10] and 5,7-dimethyl-6-nitrotetralone[11] (**37i**, **37j** and **37k**) were prepared according to the cited methods. 5-Hydroxy-6-allyltetralone (**58**),[4] prepared by the Claisen rearrangement of **37a**, was alkylated with alkyl halide in the presence of potassium carbonate to give methoxy-, butoxy-, and benzyloxytetralones (**37l**, **37m** and **37n**). In the case of **37m** and **37n**, however, the double bond was found to be isomerized to form a conjugated 1-propenyl group. Furthermore, treatment of **58** with zinc chloride gave naphthofuranone (**37o**). A naphthoxazole derivative (**37p**) was prepared from **51** by O-benzylation, reduction of the nitro group to an amino group, N-benzoylation, debenzylation, and cyclization with phosphorus pentoxide by way of compounds **59**, **60**, **61**, and **62**.

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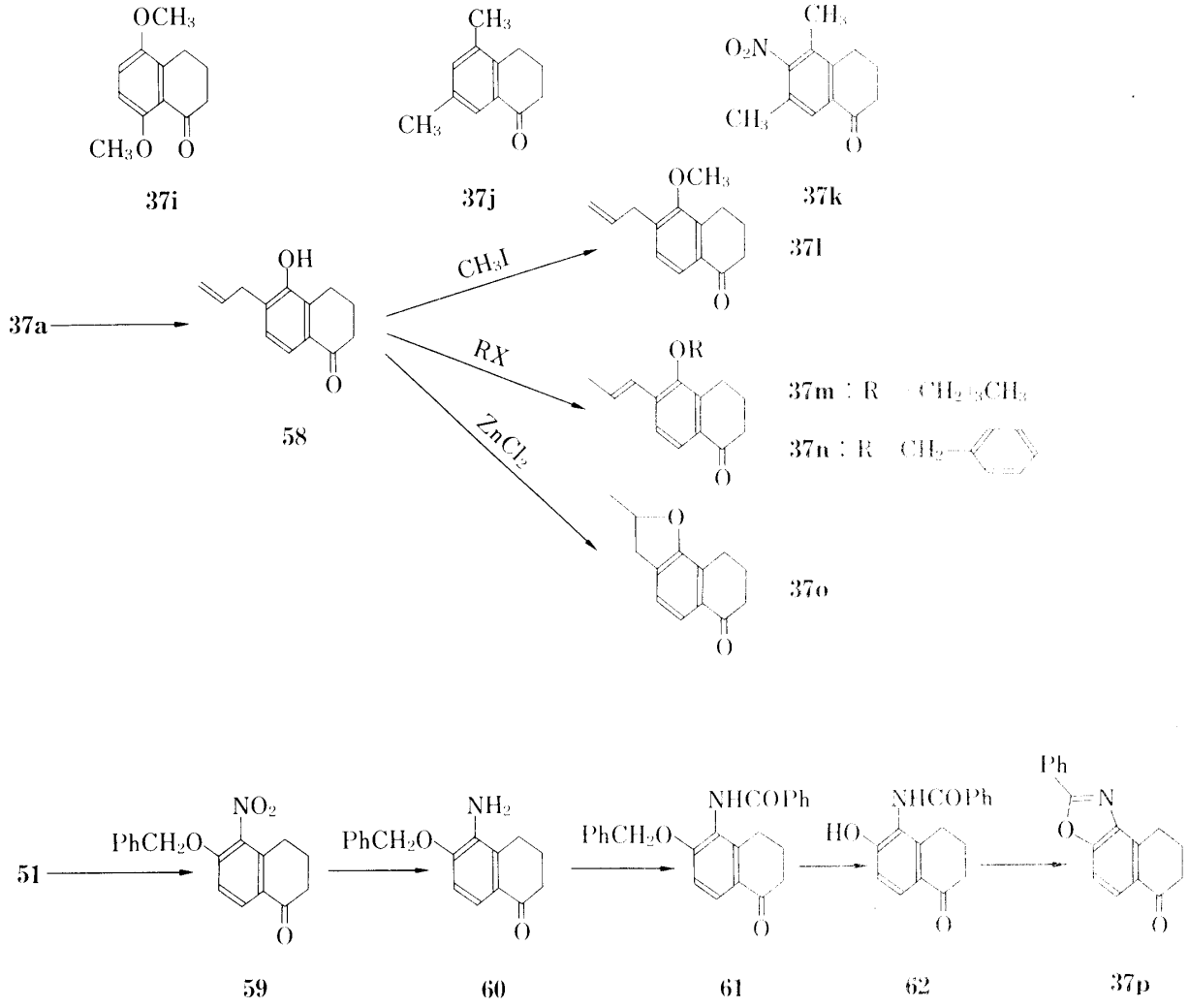

Chart 6

6-Substituted Tetralones (37q—z)

6-Aminotetralone (**63**)[12] was employed as the starting material for the synthesis of a variety of 6-substituted tetralones. Thus, the Sandmeyer reaction of **63** gave 6-chloro-(**37z**),[13] 6-bromo-(**37y**) and 6-cyano-(**37v**) tetralone, and the Gomberg Bachmann reaction afforded the 6-phenyl derivative (**37x**). Compound **37v** was led to **37w** by hydrolysis and subsequent esterification. 6-Morpholinotetralone (**37s**)[14] was also derived from **63**. 6-(*N*-Acyl-*N*-methyl)aminotetralones (**37q** and **37r**) were prepared from **63** by the same procedure as that for the 5-substituted isomer **37g**. 6-Phenoxy-(**37t**) and 6-mercaptotetralone (**68**) were prepared from 6-hydroxytetralone (**65**)[15] by procedures similar to those used for **37d** and **54**, respectively. Alkylation of **68** with butyl bromide afforded 6-butylthiotetralone (**37u**).

Biological Results

The compounds in Table I were tested for β-adrenergic blocking activity. The results are summarized in Table II. The β-blocking activity of these compounds (10^{-6} M) was measured in terms of inhibition ($-\%$) of isoproterenol-induced tachycardia in isolated atrial preparations of guinea pigs.[1] Direct cardiac action of these compounds (10^{-6} M) was also determined, and expressed in terms of the percent increase ($+\%$) in beating rate of atrial preparations.

Moderate β-adrenergic blocking activity comparable to that of practolol was found with the 5-chloro (**10a**, **10b**) and 6-chloro (**28c**) derivatives. Compound **28c** was substantially free

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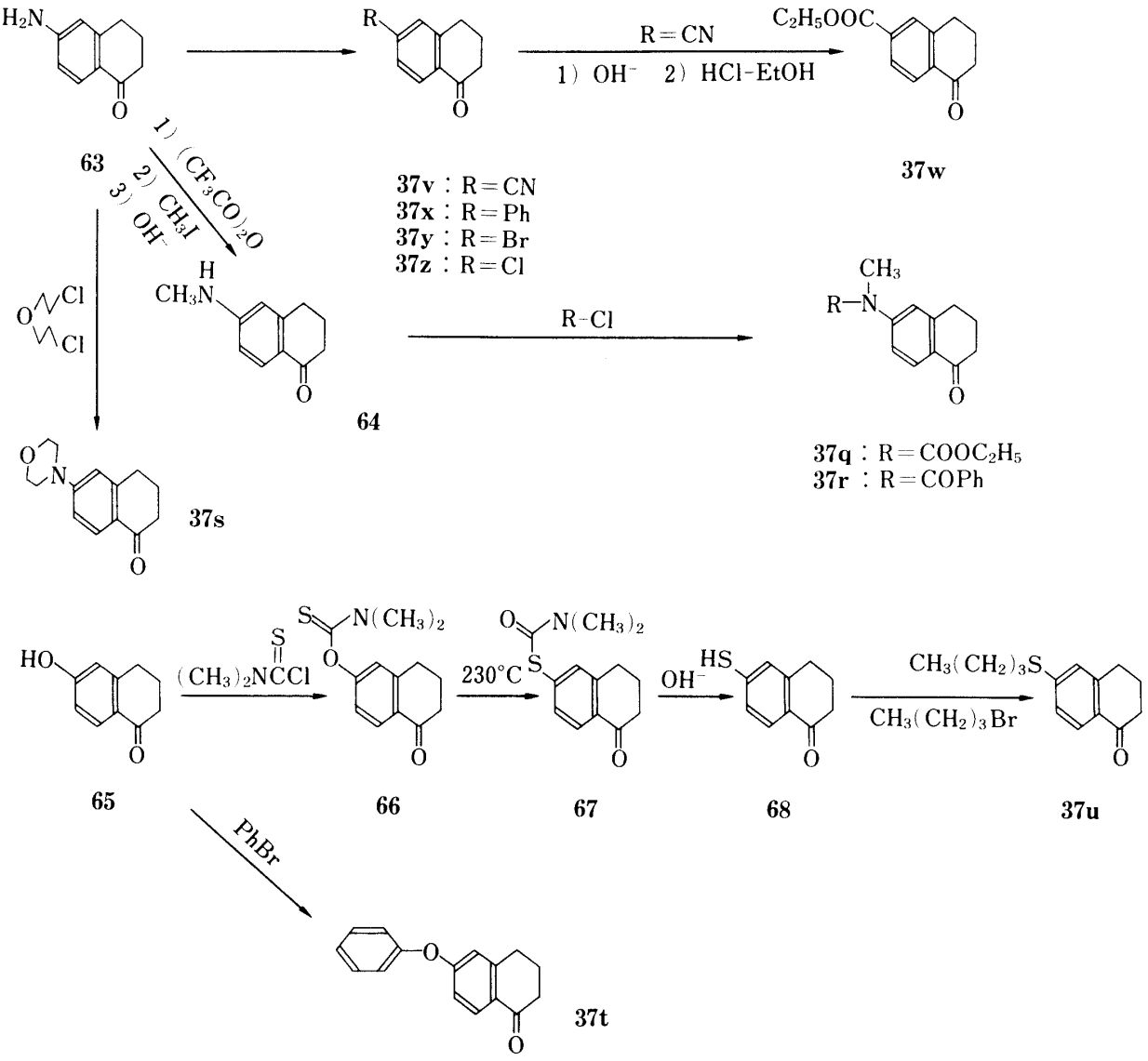

Chart 7

from cardiac stimulation activity. However, intrinsic cardiac stimulation activity to increase the beating rate of the atrial preparation was observed with **10a** and **10b**. Some of the other 5-substituted derivatives (**4**, **5**, **9**, **29**, **30**) produced tachycardia in spontaneously hypertensive rats (SHR: 30 mg/kg) after oral administration (data not shown). The finding that even derivatives without a 6-hydroxyl group showed considerable β-stimulating activity suggests that the β-agonistic property may be inherent to the 2-amino-1,2,3,4-tetrahydronaphthalen-1-ol skeleton, in accord with our previous observations.[1)]

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (a hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. The ^{1}H-NMR spectra were recorded with a Varian T-60, HA-100 or EM 390 machine with tetramethylsilane as an internal standard.

5-Butoxy-3,4-dihydro-1(2*H*)-naphthalenone (37b)——A mixture of 5-hydroxytetralone[5)] (**42**, 20 g), butyl bromide (19 g), K_2CO_3 (19 g), KI (20 g) and acetone (100 ml) was refluxed for 5 h. The insoluble material was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was taken up in AcOEt (500 ml), washed with 10% NaOH (50 ml), dried (Na_2SO_4), decolorized with activated carbon and concentrated *in vacuo* to give **37b** as a viscous

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Table II. Biological Activity

Compd. No.	β-Activity (10^{-6} M) % change in beating rate	β-Activity (10^{-6} M) % inhibition of isoproterenol (2.5×10^{-8} M) induced tachycardia
10a	+23.7±5.3	−30.7±5.8
10b	+28.9±1.6	−49.1±3.4
12a	−3.9±0.6	−8.3±2.8
13b	+2.0±3.0	−9.3±4.3
21	−0.4±0.4	−10.9±2.9
23a	−1.4±1.2	−12.4±3.8
23b	−2.2±0.8	−8.7±3.4
27b	+0.8±0.8	−14.1±4.1
28a	+5.0±2.4	−14.4±1.0
28b	+10	−15.2
28c	+4.9±4.7	−22.0±2.7
28d	+4.5±3.5	−17.6±5.4
28e	+1.3±1.8	−11.2±2.8
29	+9.7±5.5	−8.6±4.5
31a	−2.3±0.2	−11.8±2.4
Propranolol	−5.8±1.6	−62±11
Practolol	+0.9±0.9	−26±10
2[1)]	+52±4	−80±5

oil (10 g, 37%). IR ν_{max}^{neat} cm^{-1}: 1680 (C=O).

5-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (37c)——A mixture of **42** (20 g), benzyl chloride (20 g), K_2CO_3 (20 g), KI (5 g) and acetone (100 ml) was refluxed for 8 h. Work-up in a manner similar to that described for the preparation of **37b** gave **37c** as an oil (5 g, 16%). IR ν_{max}^{neat} cm^{-1}: 1680 (C=O).

5-Phenoxy-3,4-dihydro-1(2*H*)-naphthalenone (37d)——Powdered NaOMe (2.7 g) was added to a stirred mixture of **42** (8.1 g) and benzene (100 ml) under nitrogen. Next, bromobenzene (7.9 g) and CuCl (2 g) were added, and the resulting mixture was heated under reflux for 7 h. After addition of bromobenzene (8 g), reflux was continued for a further 4 h. After cooling, the reaction mixture was poured into a mixture of 10% HCl (100 ml) and AcOEt (500 ml), and filtered with celite. The organic layer of the filtrate was separated, washed (10% KOH and water), dried and concentrated *in vacuo*. The residue was chromatographed on silica gel using benzene as the eluent to give pure **37d** (3 g, 25%) as a syrup, which was crystallized from MeOH to give colorless prisms, mp 100—101 °C. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). *Anal.* Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.68; H, 5.71.

5-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone (37f)——A solution of $NaNO_2$ (74 g) in water (240 ml) was added dropwise to a stirred solution of 2-phenylaniline (**43**, 169 g) in 47% HBr (320 ml) at 0 °C. The resulting solution was added dropwise to a stirred mixture of CuBr (160 g) in 47% HBr (960 ml) at 0 °C. When the addition was complete, the solution was stirred at room temperature for 2 h. The mixture was extracted with AcOEt (300 ml × 2). The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by vacuum distillation to give 2-bromobiphenyl (**44**, 163 g, 70%) as a colorless liquid, bp 115—117 °C (5 mmHg).

A solution of **44** (23.4 g) in dry ether (50 ml) was added to a mixture of Mg (2.51 g), dry ether (100 ml) and a few chips of iodine at a rate such that refluxing continued without external heating. After the addition had been completed, *N*-methylformanilide (13.5 g) was added dropwise over a period of 1.5 h, and the resulting mixture was stirred for 1 h at room temperature. After addition of a saturated NH_4Cl solution (200 ml), the mixture was stirred for 1 h and extracted with AcOEt (200 ml). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled under a vacuum to give pure 2-phenylbenzaldehyde (**45**, 11.8 g, 65%) as a colorless liquid, bp 125—130 °C (4 mmHg).

A mixture of **45** (29 g) and $ClCH_2COOCH_3$ (20 g) was added dropwise to an $NaOCH_3$–MeOH solution [prepared from Na (5.6 g) and MeOH (80 ml)] at −5—−10 °C over a period of 2 h. After standing overnight at room temperature, the mixture was poured into ice-water (300 ml) containing AcOH (1.9 ml) and extracted with $CHCl_3$ (150 ml × 3). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in benzene (400 ml), and to this solution was added a solution of NaOMe (8.7 g) in MeOH (54 ml) at 5 °C to precipitate sodium 3-(2-biphenylyl)glycidate (**46**, 35 g, 84%) as colorless needles, mp 217 °C (dec.). *Anal.* Calcd for $C_{15}H_{11}NaO_3$: C, 68.70; H, 4.23. Found: C, 68.40; H, 4.50.

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A mixture of **46** (52 g), benzene (300 ml), water (300 ml) and AcOH (32 g) was refluxed for 3 h. After cooling, the benzene layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give 2-biphenylylacetaldehyde (**47**, 26 g, 67%) as a pale yellow liquid.

A solution of **47** (26 g) in benzene (50 ml) was added to a solution of ethoxycarbonylmethylene triphenylphosphorane (44 g) in benzene (60 ml), and the resulting mixture was refluxed for 2 h. After 50 ml of benzene had been evaporated off, petroleum ether (500 ml) was added to the mixture with stirring, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to give an oily residue, which was purified by silica gel column chromatography with benzene as the eluent to give ethyl 4-(2-biphenylyl)-2-butenoate (**48**, 28.8 g, 86%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=9 Hz, CH_3), 3.52 (2H, dd, J=9 Hz, 2 Hz, $-C\underline{H}_2CH=$), 4.20 (2H, q, J=9 Hz, $OC\underline{H}_2CH_3$), 5.75 (1H, d, J=14 Hz, $-CH=$), 7.20–7.60 (10H, m, Ph×2 and $=CH-$).

A solution of **48** (28.8 g) in AcOH (200 ml) was subjected to catalytic hydrogenation over 5% Pd-C (7 g) under atmospheric pressure at 50 °C until the absorption of H_2 ceased. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 ml), washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give ethyl 4-(2-biphenylyl)butyrate (29 g, 100%) as a viscous oil.

A solution of NaOH (9 g) in water was added to a solution of the above ester (29 g) in MeOH (150 ml), and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with water (300 ml) and extracted with ether (100 ml). The aqueous layer was acidified with conc. HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give 4-(2-biphenylyl)butyric acid (**49**, 23.6 g, 91%) as a syrup, which was heated with $AlCl_3$ (90.4 g) and NaCl (22.6 g) at 140 °C for 10 min and then for 5 min at 150 °C with stirring. Excess $AlCl_3$ was decomposed by addition of a mixture of conc. HCl and ice water under cooling, and the mixture was extracted with $CHCl_3$ (100 ml×2). The extract was evaporated *in vacuo*, and the residue was chromatographed on silica gel with benzene as the eluent to give **37f** (3.5 g, 17%) as colorless needles, mp 103–105 °C. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). *Anal.* Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.19; H, 6.44.

5-Amino-3,4-dihydro-1(2*H*)-naphthalenone (55)——A mixture of 6-hydroxy-5-nitrotetralone (**51**, 80 g),[8] K_2CO_3 (52 g) and dimethylformamide (DMF, 800 ml) was heated at 80 °C for 30 min. *N,N*-Dimethylthiocarbamoyl chloride (58 g) was added, and the mixture was stirred for 1 h at room temperature, poured into ice-water (2 l) and extracted with AcOEt (300 ml×3). The extract was washed with 10% NaOH and then water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from ether to give 6-(*N,N*-dimethylthiocarbamoyloxy)-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**52**, 80 g, 70%) as colorless prisms, mp 136–138 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.83; H, 4.70; N, 9.36.

Compound **52** (80 g) was heated in an oil bath at 170 °C for 20 min. After cooling, the residual mass was triturated with AcOEt (300 ml) to give 6-(*N,N*-dimethylcarbamoylthio)-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**53**, 80 g, 100%) as colorless crystals, mp 130–132 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.21; H, 4.97; N, 9.41.

A mixture of **53** (31 g), NaOH (8 g) and MeOH (100 ml) was refluxed for 1 h, cooled, acidified with conc. HCl, diluted with water (200 ml) and extracted with $CHCl_3$ (100 ml×3). The extract was dried (Na_2SO_4), treated with decolorizing charcoal and concentrated *in vacuo* to give 6-mercapto-5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (**54**, 23 g, 98%) as pale yellow needles, mp 113–116 °C. *Anal.* Calcd for $C_{10}H_9NO_3S$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.65; H, 4.31; N, 6.40.

A mixture of **54** (23 g), Raney nickel (wet, 120 g) and EtOH (400 ml) was refluxed for 2 h, then cooled. The Raney nickel was removed by filtration, and the filtrate was concentrated *in vacuo*. A solution of the residue in AcOEt (200 ml) was extracted with 10% HCl (200 ml×2). The aqueous layer was basified with 10% NaOH and extracted with AcOEt (100 ml×2). Evaporation of the AcOEt from the extract gave an oily residue, which was treated with 20% HCl–EtOH (10 ml) and diluted with ether (200 ml). The resulting precipitate was collected by filtration to give **55**·HCl (6.5 g, 32%) as colorless needles, mp 215–216 °C. *Anal.* Calcd for $C_{10}H_{11}NO\cdot HCl$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.50; H, 6.39; N, 6.85.

Ethyl *N*-Methyl-*N*-(1-oxo-1,2,3,4-tetrahydro-5-naphthyl)carbamate (37g)——$(CF_3CO)_2O$ (12 g) was added dropwise to a stirred mixture of **55** (6 g) and $CHCl_3$ (50 ml) at room temperature. After being stirred for 1 h, the reaction mixture was concentrated, and the residue was crystallized from MeOH to give 5-trifluoroacetylamino-3,4-dihydro-1(2*H*)-naphthalenone (**56**, 6.5 g, 83%) as colorless needles, mp 178–180 °C. *Anal.* Calcd for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92; N, 5.45. Found: C, 55.83; H, 3.76; N, 5.28.

A mixture of **56** (6.5 g), powdered KOH (3 g) and acetone (100 ml) was stirred for 30 min. After addition of CH_3I (13 g), the mixture was heated under reflux for 1 h and concentrated. A solution of KOH (5 g) in 50% EtOH (100 ml) was added to the residue, and the mixture was heated at 80 °C for 30 min, cooled and poured into water (100 ml). Extraction with AcOEt (100 ml×2) and evaporation of the solvent afforded an oily residue, which was crystallized from ether to give 5-methylamino-3,4-dihydro-1(2*H*)-naphthalenone (**57**, 3.5 g, 79%) as colorless plates, mp 101–103 °C. *Anal.* Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.63; H, 7.30; N, 8.03.

Ethyl chloroformate (4.4 g) was added dropwise to a stirred mixture of **57** (3.5 g), $CHCl_3$ (50 ml), K_2CO_3 (3.5 g) and water (30 ml). After standing overnight at ambient temperature, the $CHCl_3$ layer was washed with water, dried

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over Na_2SO_4 and concentrated *in vacuo* to give **37g** (4.5 g, 91%) as a viscous liquid. IR ν_{max}^{neat} cm^{-1}: 1685, 1730 (C=O).

5-Chloro-3,4-dihydro-1(2*H*)-naphthalenone (37h)——A solution of $NaNO_2$ (3.6 g) in water (15 ml) was added dropwise to a stirred solution of **55**·HCl (8.5 g) in 15% HCl (70 ml) 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 mixture was stirred at room temperature for 1 h, poured into water (300 ml) and extracted with AcOEt (100 ml × 2). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **37h** (6.7 g, 86%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1685 (C=O).

6-Allyl-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (37l)——A mixture of **58** (5.5 g), K_2CO_3 (10 g), CH_3I (10 ml) and DMF (30 ml) was heated at 90—100 °C for 2 h. After cooling, the mixture was diluted with water (500 ml) and extracted with AcOEt (300 ml). Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography (benzene) to give **37l** (5 g, 93%) as a colorless liquid. IR ν_{max}^{neat} cm^{-1}: 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.6 (8H, m, $CH_2 \times 4$), 3.7 (3H, s, OCH_3), 4.9—5.3 (2H, m, $=CH_2$–), 5.7—6.3 (1H, m, =CH–), 7.2 (1H, d, J=8 Hz, phenyl proton), 7.8 (1H, d, J=8 Hz, phenyl proton).

6-(1-Propenyl)-5-butoxy-3,4-dihydro-1(2*H*)-naphthalenone (37m)——A mixture of **58** (10 g), K_2CO_3 (10 g), butyl bromide (7 g) and DMF (50 ml) was heated at 100 °C for 3 h. Purification in a manner similar to that described for the preparation of **37l** gave **37m** (12 g, 94%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 6.7—7.0 (2H, m, –CH=CH–), 7.4 (1H, d, J=8 Hz, phenyl proton), 7.8 (1H, d, J=8 Hz, phenyl proton).

6-(1-Propenyl)-5-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone (37n)——A mixture of **58** (10 g), K_2CO_3 (10 g), benzyl chloride (7 g) and DMF (50 ml) was heated at 100 °C for 3 h. Work-up in a manner similar to that described for the synthesis of **37l** gave **37n** (10 g, 72%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 6.7—7.0 (2H, m, –CH=CH–), 4.8 (2H, s, $C\underline{H}_2Ph$).

2-Methyl-2,3,8,9-tetrahydro-6(7*H*)-naphtho[1,2-*b*]furanone (37o)——A mixture of **58** (10 g), AcOH (60 ml), conc. HCl (30 ml) and $ZnCl_2$ (9 g) was heated at 100—110 °C for 16 h. After cooling, the mixture was diluted with a mixture of AcOEt (500 ml) and water (500 ml). The AcOEt layer was washed with 10% NaOH and water, dried over Na_2SO_4, decolorized with activated carbon, and concentrated *in vacuo*. The residual brown oil was purified by silica gel column chromatography (acetone : benzene = 1 : 30) to afford **37o** (4.5 g) as a viscous oil, which was crystallized from petroleum ether to give pale yellow prisms. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.5 (3H, d, J= 6 Hz, O–CH–$C\underline{H}_3$). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.13; H, 6.77.

2-Phenyl-8,9-dihydro-6(7*H*)-naphth[1,2-*d*]oxazolone (37p)——Benzoyl chloride (6.2 g) was added to a stirred mixture of 6-benzyloxy-5-amino-3,4-dihydro-1(2*H*)-naphthalenone[16] (**60**, 10 g), $CHCl_3$ (200 ml), K_2CO_3 (5 g) and water (40 ml) at ambient temperature. Stirring was continued for 2 h, then the $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from MeOH and the resulting colorless needles were collected by filtration to give 5-benzoylamino-6-benzyloxy-1(2*H*)-naphthalenone (**61**, 13.4 g, 96%), mp 210—211 °C. *Anal.* Calcd for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.47; H, 5.86; N, 3.64.

A solution of **61** (5 g) in MeOH (250 ml) was subjected to catalytic hydrogenolysis over 5% Pd-C (2.5 g) at room temperature under atmospheric pressure. After hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from AcOEt to give 5-benzoylamino-6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**62**, 3 g, 79%) as colorless needles, mp 118—120 °C. *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.70; H, 5.49; N, 4.71.

A mixture of **62** (0.5 g), xylene (20 ml) and P_2O_5 (0.5 g) was stirred at 150 °C for 2 h, then cooled. AcOEt (100 ml) was added to the mixture, and the resulting solution was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Recrystallization of the residue from petroleum ether gave **37p** (0.4 g, 64%) as colorless needles, mp 143—145 °C. *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.61; H, 4.75; N, 5.09.

Ethyl *N*-Methyl-*N*-(1-oxo-1,2,3,4-tetrahydro-6-naphthyl)carbamate (37q)——6-Amino-3,4-dihydro-1(2*H*)-naphthalenone[12] (**63**, 16 g) was trifluoroacetylated similarly to the case of **56** to yield 6-trifluoroacetylamino-3,4-dihydro-1(2*H*)-naphthalenone (22 g, 86%) as colorless crystals. *Anal.* Calcd for $C_{12}H_{10}FNO_2$: C, 56.04; H, 3.92; N, 5.45. Found: C, 56.17; H, 3.70; N, 5.30.

This compound (22 g) was methylated similarly to the case of **57** to give 6-methylamino-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride (**64**·HCl, 11 g, 61%) as colorless plates, mp 155—158 °C. *Anal.* Calcd for $C_{11}H_{13}NO \cdot HCl$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.15; H, 6.56; N, 6.70.

Ethoxycarbonylation of **64** (3.5 g) in a manner similar to that described for the preparation of **37g** gave **37q** (3.5 g, 86%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1680, 1730 (C=O).

***N*-Methyl-*N*-(1-oxo-1,2,3,4-tetrahydro-6-naphthyl)benzamide (37r)**——Benzoylation of **64** (11 g) in a manner similar to that described for **61** gave **37r** (10 g, 67%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (C=O).

6-Phenoxy-3,4-dihydro-1(2*H*)-naphthalenone (37t)——The reaction of 6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone[15] (**65**, 48 g) and bromobenzene (80 g) in the presence of NaOMe by a procedure similar to that described for the synthesis of **37d** gave **37t** (9.7 g, 14%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1680 (C=O).

6-Butylthio-3,4-dihydro-1(2*H*)-naphthalenone (37u)——The reaction of **65** (16 g) with *N*,*N*-dimethylthiocarbamoyl chloride (15 g) by a procedure similar to that used for the synthesis of **52** and crystallization of the product from ether gave 6-(*N*,*N*-dimethylthiocarbamoyloxy)-3,4-dihydro-1(2*H*)-naphthalenone (**66**, 12.5 g, 51%) as col-

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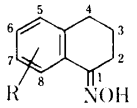
TABLE III. 3,4-Dihydro-1(2*H*)-naphthalenone Oximes (**38**)



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
38a	5-$OCH_2CH=CH_2$	91	90—92	$C_{13}H_{15}NO_2$	71.86 (71.52	6.96 6.74	6.45 6.38)
38b	5-$O(CH_2)_3CH_3$	56	131—134	$C_{14}H_{19}NO_2$	72.07 (72.21	8.21 8.37	6.00 5.76)
38c	5-OCH_2Ph	94	124—126	$C_{17}H_{17}NO_2$	76.38 (76.28	6.41 6.45	5.24 5.17)
38d	5-OPh	94	133—136	$C_{16}H_{15}NO_2$	75.87 (75.36	5.97 5.68	5.53 5.17)
38e	5-$COOC_2H_5$	78	90—91	$C_{13}H_{15}NO_3$	66.93 (66.78	6.48 6.61	6.01 5.75)
38f	5-Ph	93	161—163	$C_{16}H_{15}NO$	80.98 (80.69	6.37 6.42	5.90 5.86)
38g	5-$N(CH_3)COOC_2H_5$	84	165—167	$C_{14}H_{18}N_2O_3$	64.10 (64.32	6.92 6.75	10.68 10.44)
38h	5-Cl	96	115—117	$C_{10}H_{10}ClNO$	61.39 (61.03	5.15 5.35	7.16 6.84)
38j	5-CH_3 7-CH_3	90	145—148	$C_{12}H_{15}NO$	76.15 (76.16	7.99 7.96	7.40 7.43)
38k	5-CH_3 6-NO_2 7-CH_3	87	198—199	$C_{12}H_{14}N_2O_3$	61.52 (61.59	6.02 6.12	11.96 11.76)
38l	5-OCH_3 6-$CH_2CH=CH_2$	86	108—111	$C_{14}H_{17}NO_2$	72.70 (72.89	7.41 7.50	6.06 5.60)
38m	5-$O(CH_2)_3CH_3$ 6-$CH=CHCH_3$	95	120—123	$C_{17}H_{23}NO_2$	74.69 (74.72	8.48 8.58	5.12 5.15)
38n	5-OCH_2Ph 6-$CH=CHCH_3$	81	126—129	$C_{20}H_{21}NO_2$	78.14 (77.94	6.89 6.97	4.56 4.62)
38o	5,6-$OCH(CH_3)CH_2$–	93	150—152	$C_{13}H_{15}NO_2$	71.86 (71.78	6.96 6.99	6.45 6.37)
38p	5,6-$N=C(Ph)O$–	82	233—234	$C_{17}H_{14}N_2O_2$	73.36 (73.10	5.07 4.78	10.07 10.20)
38q	6-$N(CH_3)COOC_2H_5$	81	Oil	[a]			
38r	6-$N(CH_3)COPh$	71	167—168	$C_{18}H_{18}N_2O_2$	73.45 (73.30	6.16 5.93	9.52 9.45)
38t	6-OPh	83	204—206	$C_{16}H_{15}NO_2$	75.87 (75.53	5.97 5.77	5.53 5.60)
38u	6-$S(CH_2)_3CH_3$	77	101—103	$C_{14}H_{19}NOS$	67.44 (67.30	7.68 7.46	5.62 5.40)
38v	6-CN	93	189—191	$C_{11}H_{10}N_2O$	70.95 (70.81	5.41 5.25	15.05 15.03)
38w	6-$COOC_2H_5$	78	127—128	$C_{13}H_{15}NO_3$	66.93 (66.75	6.48 6.51	6.01 6.18)
38x	6-Ph	83	164—165	$C_{16}H_{15}NO$	80.98 (80.73	6.37 6.45	5.90 5.72)
38y	6-Br	66	144—146	$C_{10}H_{10}BrNO$	50.02 (49.80	4.20 4.51	5.84 5.63)
38z	6-Cl	80	143—145	$C_{10}H_{10}ClNO$	61.39 (61.30	5.15 5.36	7.16 7.00)

a) Used for the next step without purification.

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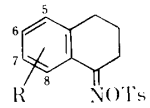
TABLE IV. 3,4-Dihydro-1(2*H*)-naphthalenone *O*-Tosyloximes (**39**)



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
39a	5-$OCH_2CH=CH_2$	95	73—74	$C_{20}H_{21}NO_4S$	64.68 (64.43	5.70 5.71	3.77 3.59)
39b	5-$O(CH_2)_3CH_3$	66	73—74	$C_{21}H_{25}NO_4S$	65.10 (65.16	6.50 6.45	3.62 3.84)
39c	5-OCH_2Ph	66	Oil	*a)*			
39d	5-OPh	97	107—109	$C_{23}H_{21}NO_4S$	67.80 (68.14	5.20 5.24	3.44 3.29)
39e	5-$COOC_2H_5$	92	129—131	$C_{20}H_{21}NO_5S$	62.01 (61.79	5.46 5.59	3.62 3.40)
39f	5-Ph	79	158—160	$C_{23}H_{21}NO_3S$	70.57 (70.41	5.41 5.67	3.58 3.39)
39g	5-$N(CH_3)COOC_2H_5$	93	Oil	*a)*			
39h	5-Cl	74	105—107	$C_{17}H_{16}ClNO_3S$	58.38 (58.51	4.61 4.50	4.01 3.73)
39j	5-CH_3 7-CH_3	97	131—134	$C_{19}H_{21}NO_3S$	66.46 (66.70	6.16 6.17	4.08 4.55)
39k	5-CH_3 6-NO_2 7-CH_3	97	148—150	$C_{19}H_{20}N_2O_5S$	58.76 (58.58	5.19 5.11	7.21 7.01)
39l	5-OCH_3 6-$CH_2CH=CH_2$	95	Oil	*a)*			
39m	5-$O(CH_2)_3CH_3$ 6-$CH=CH-CH_3$	96	Oil	*a)*			
39n	5-OCH_2Ph 6-$CH=CH-CH_3$	97	Oil	*a)*			
39o	5,6-$OCH(CH_3)CH_2$–	97	65—70	$C_{20}H_{21}NO_4S \cdot 1/2C_6H_6$	67.31 (68.77	5.89 5.82	3.41 3.40)
39p	5,6-$N(Ph)=C-O$–	61	178—180	$C_{24}H_{20}N_2O_4S$	66.66 (66.38	4.66 4.47	6.48 6.50)
39q	6-$N(CH_3)COOC_2H_5$	94	Oil	*a)*			
39r	6-$N(CH_3)COPh$	83	201—203	$C_{25}H_{24}N_2O_4S$	66.65 (66.34	5.39 5.51	6.25 6.24)
39t	6-Ph	97	125—127	$C_{23}H_{21}NO_4S$	67.80 (67.65	5.20 4.93	3.44 3.31)
39u	6-$S(CH_2)_3CH_3$	88	89—91	$C_{21}H_{25}NO_3S_2$	62.52 (62.09	6.25 6.38	3.47 3.36)
39v	6-CN	93	161—163	$C_{18}H_{16}N_2O_3S$	63.52 (63.41	4.74 4.96	8.23 8.05)
39w	6-$COOC_2H_5$	79	155—157	$C_{20}H_{21}NO_5S$	62.01 (61.85	5.46 5.61	3.62 3.49)
39x	6-Ph	96	165—167	$C_{23}H_{21}NO_3S$	70.57 (70.66	5.41 5.63	3.58 3.40)
39y	6-Br	69	145—146	$C_{17}H_{16}BrNO_3S$	51.79 (51.96	4.09 3.73	3.55 3.35)
39z	6-Cl	89	143—144	$C_{17}H_{16}ClNO_3S$	58.38 (58.20	4.61 4.75	4.01 3.76)

a) Used for the next step without purification.

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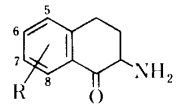
TABLE V. 2-Amino-3,4-dihydro-1(2*H*)-naphthalenones (**40**)



Compd. No.	R	Yield (%) (Form)	mp (°C) dec.	Formula	Analysis (%) Calcd (Found)		
					C	H	N
40a	5-$OCH_2CH=CH_2$	66 (HCl)	170—180	$C_{13}H_{15}NO_2 \cdot HCl$	61.53 (61.41)	6.36 6.42	5.52 5.58)
40b	5-$O(CH_2)_3CH_3$	39 (HCl)	170—180	$C_{14}H_{19}NO_2 \cdot HCl$	62.32 (61.89)	7.47 7.56	5.19 5.29)
40c	5-OCH_2Ph	46 (HCl)	>170	$C_{17}H_{17}NO_2 \cdot HCl$	67.21 (66.83)	5.97 6.12	4.61 4.84)
40d	5-OPh	56 (HCl)	170—180	$C_{16}H_{15}NO_2 \cdot HCl$	62.43 (62.52)	5.90 5.86	4.55 4.53)
40e	5-$COOC_2H_5$	62 (HCl)	214	$C_{13}H_{15}NO_3 \cdot HCl$	57.89 (57.93)	5.98 5.76	5.19 5.38)
40f	5-Ph	59 (HCl)	240—242	$C_{16}H_{15}NO \cdot HCl$	62.85 (62.60)	5.28 5.41	4.58 4.40)
40g	5-$N(CH_3)COOC_2H_5$	— (HCl)	Oil	a)			
40h	5-Cl	65 (HCl)	236	$C_{10}H_{10}ClNO \cdot HCl \cdot H_2O$	48.02 (47.85)	5.24 5.44	5.60 5.73)
40i	5-OCH_3 8-OCH_3	73 (HCl)	240—250	$C_{12}H_{15}NO_3 \cdot HCl$	55.93 (55.91)	6.26 6.16	5.44 5.36)
40j	5-CH_3 7-CH_3	40 (HCl)	190—200	$C_{12}H_{15}NO \cdot HCl \cdot H_2O$	59.14 (59.23)	7.45 7.42	5.75 5.92)
40k	5-CH_3 6-NO_2 7-CH_3	49 (HCl)	170—190	$C_{12}H_{14}N_2O_3 \cdot HCl \cdot H_2O$	49.92 (50.03)	5.93 5.80	9.70 9.71)
40l	5-OCH_3 6-$CH_2CH=CH_2$	59 (HCl)	170—180	$C_{14}H_{17}NO_2 \cdot HCl$	62.80 (62.56)	6.78 6.76	5.23 5.15)
40m	5-$O(CH_2)_2CH_3$ 6-$CH=CH-CH_3$	53	Oil	a)			
40n	5-OCH_2Ph 6-$CH=CH-CH_3$	46 (HCl)	154—157	$C_{20}H_{21}NO_2 \cdot HCl$	69.65 (69.72)	6.43 6.46	4.06 3.96)
40o	5,6-$OCH(CH_3)CH_2-$	51 (HCl)	181—184	$C_{13}H_{15}NO_2 \cdot HCl$	61.54 (61.39)	6.36 6.48	5.52 5.54)
40p	5,6-$N=C(Ph)-O-$	74 (HCl)	230	$C_{17}H_{14}N_2O_2 \cdot HCl \cdot H_2O$	61.36 (61.49)	5.15 5.01	8.42 8.69)
40q	6-$N(CH_3)COOC_2H_5$	45 (HCl)	205	$C_{14}H_{17}N_2O_3 \cdot HCl$	56.47 (56.65)	6.09 6.13	9.41 9.09)
40r	6-$N(CH_3)COPh$	— (HCl)	Oil	a)			
40s	6-N⟨O⟩	72 (HCl)	>200	$C_{14}H_{18}N_2O_2 \cdot HCl$	59.46 (58.99)	6.77 6.78	9.91 9.89)
40t	6-OPh	— (HCl)	Oil	a)			
40u	6-$S(CH_2)_3CH_3$	52 (HCl)	182—184	$C_{14}H_{19}NOS \cdot HCl$	58.84 (58.90)	7.05 7.29	4.90 4.68)
40v	6-CN	84 (HCl)	220—225	$C_{11}H_{10}N_2O \cdot HCl$	59.33 (59.30)	4.98 5.11	12.58 12.42)
40w	6-$COOC_2H_5$	76 (HCl)	218—220	$C_{13}H_{15}NO_3 \cdot HCl$	57.89 (57.96)	5.98 5.70	5.19 4.88)
40x	6-Ph	50 (HCl)	235	$C_{16}H_{15}NO \cdot HCl$	62.85 (62.90)	5.28 5.35	4.58 4.22)

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TABLE V. continued.

Compd. No.	R	Yield (%) (Form)	mp (°C) dec.	Formula	Analysis (%) Calcd (Found) C	H	N
40y	6-Br	43 (HCl)	210—215	$C_{10}H_{10}BrNO \cdot HCl$	43.42 (42.95	4.01 4.38	5.06 5.30)
40z	6-Cl	74 (HCl)	227	$C_{10}H_{10}ClNO \cdot HCl$	51.72 (51.93	5.64 5.65	6.03 6.01)

a) Used for next step without purification.

orless needles, mp 132—134 °C. *Anal.* Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 5.85; N, 5.47.

Compound **66** (18.7 g) was heated in an oil bath at 230 °C for 30 min, then cooled and triturated with ether (200 ml) to give 6-(*N*,*N*-dimethylcarbamoylthio)-3,4-dihydro-1(2*H*)-naphthalenone (**67**, 15 g, 80%) as colorless prisms, mp 95—97 °C. *Anal.* Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.70; H, 6.19; N, 5.38.

Compound **67** (15 g) was hydrolyzed with NaOH (5 g) in MeOH (50 ml) similarly to the case of **54** to give 6-mercapto-3,4-dihydro-1(2*H*)-naphthalenone (**68**, 10 g, 93%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1690 (C=O).

A mixture of **68** (10 g), butyl bromide (13 g), powdered NaOMe (5 g) and MeOH (50 ml) was stirred for 3 h at room temperature. The mixture was diluted with ice-water (200 ml), acidified with conc. HCl and extracted with AcOEt (200 ml). The extract was concentrated and the residue was purified with silica gel column chromatography (benzene) to give **37u** (8.5 g, 65%) as a colorless liquid.

1-Oxo-1,2,3,4-tetrahydro-6-naphthyl Cyanide (37v)——A solution of $NaNO_2$ (6.9 g) in water (20 ml) was added dropwise to a solution of **63** (16 g) in 5% HCl (60 ml) with stirring at 0 °C. The resulting solution was added to a stirred mixture of $CuSO_4$ (25 g), KCN (28 g) and water (200 ml) at 0 °C. The mixture was stirred for 2 h, poured into water (200 ml) and extracted with AcOEt (200 ml × 2). The extract was washed with water, dried over Na_2SO_4, decolorized with activated carbon and concentrated to give **37v** (10.5 g, 62%) as colorless needles, mp 129—130 °C. *Anal.* Calcd for $C_{11}H_{19}NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.01; H, 5.57; N, 8.05.

Ethyl 1-Oxo-1,2,3,4-tetrahydro-6-naphthoate (37w)——A mixture of **37v** (20 g), KOH (10 g) and 80% EtOH (250 ml) was heated under reflux for 4 h. After evaporation of the EtOH, the remaining aqueous solution was acidified with 10% HCl, and the resulting precipitate was collected by filtration to give 1-oxo-1,2,3,4-tetrahydro-6-naphthoic acid (8.5 g, 38%).

This compound (8.5 g) was added to 20% HCl–EtOH (200 ml) and the mixture was refluxed for 3 h. Evaporation of the solvent gave an oily residue, which was purified by silica gel column chromatography with benzene as the eluent to give **37w** (6 g, 62%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1720, 1780 (C=O).

6-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone (37x)——A solution of $NaNO_2$ (3.8 g) in water (5 ml) was added dropwise to a solution of **63** (8 g) in conc. HCl (15 ml) at 0 °C. The resulting solution was added dropwise to a vigorously stirred mixture of benzene (200 ml), NaOAc (16 g) and water (40 ml). Stirring was continued overnight, then the benzene layer was washed with water and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with benzene as the eluent to give **37x** as an oil, which was crystallized from a mixture of ether and petroleum ether to give colorless prisms (2.3 g, 21%), mp 105—107 °C. *Anal.* Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.37; H, 6.17.

6-Bromo-3,4-dihydro-1(2*H*)-naphthalenone (37y)——A solution of $NaNO_2$ (9.2 g) in water (30 ml) was added dropwise to a solution of **63** (20 g) in 25% HBr (60 ml) at 0 °C. The resulting solution was added to a stirred mixture of CuBr (20 g) and 47% HBr (120 ml) at 0 °C. The whole was stirred for 2 h at room temperature, diluted with water (200 ml) and extracted with AcOEt (200 ml × 2). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **37y** (20 g, 72%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1685 (C=O).

3,4-Dihydro-1(2*H*)-naphthalenone Oximes (38, Table III)——General Procedure: K_2CO_3 (10 g) and $NH_2OH \cdot HCl$ (10 g) were added to a solution of tetralone derivative (**37**, 10 g) in MeOH (100 ml) and water (10 ml). The mixture was refluxed for 3 h with stirring. After cooling, the mixture was poured into water (500 ml). The resulting precipitate was collected by filtration, washed with water and recrystallized from 50% MeOH to give **38** as colorless prisms. Compound **38q** was obtained as an oil, which was used in the next step without purification.

3,4-Dihydro-1(2*H*)-naphthalenone *O*-Tosyloximes (39, Table IV)——General Procedure: *p*-Toluenesulfonyl chloride (15 g) was added portionwise to an ice-cooled solution of **38** (10 g) in pyridine (50 ml). When the addition was complete, the mixture was stirred for 30 min at 5 °C and for a further 1 h at room temperature, and then poured into ice-water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from MeOH

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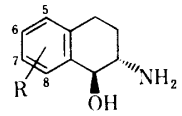
TABLE VI. *trans*-2-Amino-1,2,3,4-tetrahydronaphthalen-1-ols (**41**)



Compd. No.	R	Yield (%)	Form	mp (°C) dec.	Formula	Analysis (%) Calcd (Found)			NMR C_1–H δ (J)[a]
						C	H	N	
41a	5-$OCH_2CH=CH_2$	44	HCl	193—198	$C_{13}H_{17}NO_2 \cdot HCl$	61.05 (61.07	7.09 7.08	5.48 5.52)	—
41b	5-$O(CH_2)_3CH_3$	66	HCl	133—136	$C_{14}H_{21}NO_2 \cdot HCl$	61.86 (61.88	8.16 8.17	5.15 5.35)	4.7[b] (7.5)
41c	5-OCH_2Ph	71	Base	139—141	$C_{17}H_{19}NO_2$	75.81 (75.79	7.11 7.09	5.20 5.35)	—
41d	5-OPh	63	HCl	230—240	$C_{16}H_{17}NO_2 \cdot HCl$	65.86 (65.59	6.22 5.74	4.80 4.64)	4.7[b] (7.5)
41e	5-$COOC_2H_5$	79	HCl	168—170	$C_{13}H_{17}NO_3 \cdot HCl$	57.46 (57.40	6.68 6.90	5.16 5.33)	4.7[b] (8)
41f	5-Ph	68	HCl	283—285	$C_{16}H_{17}NO \cdot HCl$	69.68 (69.80	6.58 6.73	5.08 4.76)	4.8[b] (8)
41g	5-$N\begin{smallmatrix}CH_3\\COOC_2H_5\end{smallmatrix}$	46[d]	HCl	142—145	$C_{14}H_{19}N_2O_3 \cdot HCl$	56.09 (55.83	6.72 6.57	9.35 9.17)	4.7[b] (8)
41h	5-Cl	62	HCl	264—265	$C_{10}H_{12}ClNO \cdot HCl$	51.30 (51.09	5.60 5.48	5.98 6.13)	4.7[b] (8)
41i	5-OCH_3 8-OCH_3	51	Fumarate	205—210	$C_{12}H_{17}NO_3 \cdot 1/2C_4H_4O_4 \cdot 1/2H_2O$	57.92 (57.60	6.94 6.70	4.83 4.70)	—
41j	5-CH_3 7-CH_3	52	Base	156—159	$C_{12}H_{17}NO$	75.35 (75.37	8.90 9.02	7.32 7.20)	4.3[c] (7.5)
41k	5-CH_3 6-NO_2 7-CH_3	86	Base	156—158	$C_{12}H_{16}N_2O_3$	61.00 (61.33	6.83 6.50	11.86 11.84)	4.6[c] (6)
41l	5-OCH_3 6-$CH_2CH=CH_2$	40	HCl	190—195	$C_{14}H_{25}NO_2 \cdot HCl$	62.33 (62.15	7.47 7.42	5.19 5.05)	4.7[b] (7)

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41m	5-O$(CH_2)_3CH_3$ 6-CH=$CHCH_3$	13	HCl	120—123	$C_{17}H_{25}NO_2 \cdot HCl$	65.48 (65.30	8.40 8.46	4.49 4.59)	4.4[b] (7)
41n	5-OCH_2Ph 6-CH=$CHCH_3$	60	Base	130—133	$C_{20}H_{23}NO_2$	77.64 (77.61	7.49 7.49	4.53 4.40)	—
41o	5,6-O$\overset{\overset{CH_3}{\vert}}{C}HCH_2$–	34	HCl	229—231	$C_{13}H_{17}NO_2 \cdot HCl$	61.06 (61.21	7.10 7.34	5.48 5.42)	4.6[b] (7)
41p	5,6-N=$\overset{\overset{Ph}{\vert}}{C}$–O–	71	HCl	280—282	$C_{17}H_{16}N_2O_2 \cdot HCl$	64.45 (64.29	5.41 5.70	8.84 8.56)	4.7[b] (8)
41q	6-N$\overset{CH_3}{\underset{COOC_2H_5}{}}$	88	HCl	195—197	$C_{14}H_{19}N_2O_3 \cdot HCl$	56.07 (56.00	6.72 6.85	9.35 9.09)	4.7[b] (8)
41r	6-N$\overset{CH_3}{\underset{COPh}{}}$	42[d]	HCl	216—218	$C_{18}H_{20}N_2O_2 \cdot HCl$	64.95 (64.78	6.36 6.10	8.41 8.63)	4.7[b] (8)
41s	6-N⟨ O⟩	35	HCl	195—215	$C_{14}H_{20}N_2O_2 \cdot 2HCl$	52.34 (51.92	6.90 6.94	8.72 8.73)	4.7[b] (8)
41t	6-OPh	45[d]	HCl	220—222	$C_{16}H_{17}NO_2 \cdot HCl$	65.86 (65.73	6.22 6.05	4.80 4.67)	4.6[b] (8)
41u	6-S$(CH_2)_3CH_3$	78	HCl	208—209	$C_{14}H_{21}NOS \cdot HCl$	58.43 (58.27	7.71 7.60	4.87 4.95)	4.6[b] (8)
41v	6-CN	69	HCl	>300	$C_{11}H_{12}N_2O \cdot HCl$	58.80 (58.71	5.83 5.63	12.47 12.58)	4.7[b] (8)
41w	6-$COOC_2H_5$	79	HCl	262—264	$C_{13}H_{17}NO_3 \cdot HCl$	57.46 (57.66	6.68 6.45	5.16 4.90)	4.6[b] (8)
41x	6-Ph	65	HCl	285—286	$C_{16}H_{17}NO \cdot HCl$	69.68 (69.50	6.58 6.45	5.06 5.20)	4.65[b] (7)
41y	6-Br	40	HCl	217—220	$C_{10}H_{12}BrNO \cdot HCl$	43.11 (42.89	4.70 4.85	5.03 5.11)	4.6[b] (7)
41z	6-Cl	92	HCl	233—235	$C_{10}H_{12}ClNO \cdot HCl$	51.32 (51.09	5.60 5.93	5.99 5.88)	4.6[b] (8)

a) Expressed in Hz. *b*) In d_6-DMSO. *c*) In $CDCl_3$. *d*) Based on *O*-tosyloxime.

In DMSO-d_6.

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or $CHCl_3$–petroleum ether to give **39** as colorless prisms. In the cases of **39c**, **39g**, **39l**, **39m**, **39n** and **39q**, where the tosyloximes were not crystallized, the mixture was extracted with AcOEt (200 ml × 2) and the oily residue obtained by evaporation of the extract was used for the subsequent step without further purification.

2-Amino-3,4-dihydro-1(2*H*)-naphthalenones (40, Table V)——General Procedure: A solution of KOEt in EtOH, prepared from K (0.055 mol) and abs. EtOH (30 ml), was added to a chilled solution of **39** (0.05 mol) in benzene (300 ml) under nitrogen. When the addition was complete, the reaction mixture was stirred for 5 h then allowed to stand for 1 week in a refrigerator. The deposited insoluble material was removed by filtration, and conc. HCl (25 ml) was added to the filtrate, which was then diluted with ether (200 ml). The resulting crystals were collected by filtration and recrystallized from EtOH (200 ml) to give **40**·HCl as colorless needles. In the cases of **40g**, **40m**, **40r** and **40t**, where the hydrochlorides were not crystallized, the conc. HCl layer was separated and the organic 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 (41, Table VI)**——General Procedure: $NaBH_4$ (2 g) was added portionwise to a stirred solution of **40**·HCl (2 g) in MeOH (50 ml) 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 over Na_2SO_2 and concentrated *in vacuo*. In the cases of **41c**, **41j**, **41k** and **41n**, the residue was recrystallized from ether–petroleum ether to give colorless prisms. Compound **41i** was isolated as colorless crystals of the fumarate. In other cases, the residue was dissolved in ether (50 ml), and 20% ethanolic HCl (5 ml) was added to the solution to deposit the hydrochloride, which was recrystallized from MeOH–ether to give colorless prisms.

***trans*-2-(*N*-Substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (3—28, Table I)**——General Procedure: $NaBH_3CN$ (1 g) was added portionwise to a stirred solution of **41**·HCl (1 g) and ketone (2—5 g) in MeOH (30 ml) at 5 °C.[17] 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 over Na_2SO_4 and concentrated *in vacuo* to give the desired compounds (**3**—**28**), each as a viscous oil, which was led to the crystalline hydrochloride or fumarate by addition of ethanolic HCl or a saturated ethereal solution of fumaric acid, respectively, in ethereal solution.

***trans*-2-Benzhydrylamino-6-butylthio-1,2,3,4-tetrahydronaphthalen-1-ol (23c, Table I)**——A mixture of **41u**·HCl (0.6 g), CH_3CN (60 ml), benzhydryl chloride (1.2 g), Et_3N (1 g) and KI (0.5 g) was refluxed for 20 h with stirring. After removal of insoluble material by filtration, the solvent was evaporated off. The residue was chromatographed on silica gel (acetone : benzene = 1 : 20) to give **23c** as an oil, which yielded colorless needles of the hydrochloride (0.24 g) upon treatment with 20% ethanolic HCl (2 ml) followed by dilution with ether.

2-Acetamido-5,8-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (70)——A mixture of 5,8-dimethoxy-2-nitro-3,4-dihydro-1(2*H*)-naphthalenone[3] (**69**, 4.3 g), AcOH (50 ml) and Ac_2O (25 ml) was subjected to catalytic hydrogenation over Raney nickel (wet, 5 g) at ambient temperature and pressure. After 1 l of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was diluted with water (500 ml). The mixture was extracted with $CHCl_3$ (150 ml × 2) and the extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in MeOH (100 ml), decolorized with activated carbon, concentrated to half the initial volume and diluted with ether (100 ml) to precipitate **70** (2.5 g, 57%) as colorless needles, mp 185—186 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH); 1680, 1640 (C=O). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.63; H, 6.36; N, 5.28.

2-Amino-5,8-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone (40i, Table V)——A mixture of **70** (2.5 g) and 4 N HCl (90 ml) was heated for 2 h. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH (500 ml) and decolorized with activated carbon. Concentration of the solution gave **40i**·HCl (1.8 g, 73%) as colorless needles.

2-Formyl-6-morpholino-3,4-dihydro-1(2*H*)-naphthalenone (71)——A solution of **37s** (2.31 g) in benzene (50 ml) was added to a stirred mixture of powdered NaOMe (2.6 g), HCOOEt (2.96 g) and benzene (200 ml) under nitrogen at 5 °C. After being stirred for 1 h at room temperature under nitrogen, the mixture was diluted with water (500 ml), acidified with conc. HCl, and extracted with AcOEt (200 ml). The extract was dried over Na_2SO_4 and evaporated *in vacuo*. Crystallization of the residue from MeOH gave **71** (2 g, 77%) as yellow prisms, mp 130—132 °C. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.67; N, 5.41.

2-Hydroxyimino-6-morpholino-3,4-dihydro-1(2*H*)-naphthalenone (72)——A solution of $NaNO_2$ (3.08 g) in water (20 ml) was added dropwise to a stirred mixture of **71** (10.5 g), CH_2Cl_2 (100 ml), AcOH (100 ml) and water (10 ml) at 0 °C. When the addition was complete, the mixture was stirred for a further 1 h at 0 °C, diluted with water (1.5 l), neutralized with $NaHCO_3$ and extracted with AcOEt (500 ml × 3). The extract was washed with water, dried over Na_2SO_4 and concentrated. The deposited yellow prisms were collected by filtration to give **72** (9 g, 85%), mp 160—190 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 65.10; H, 6.06; N, 10.39.

2-Amino-6-morpholino-3,4-dihydro-1(2*H*)-naphthalenone (40s, Table V)——A solution of **72** (9.5 g) in MeOH (200 ml) containing conc. HCl (20 ml) was hydrogenated over 10% Pd-C (2 g) at ambient temperature and pressure until the absorption of hydrogen ceased. The mixture was diluted with water (200 ml) and the catalyst was removed

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by filtration. The filtrate was concentrated *in vacuo*, and the residue was dissolved in MeOH (100 ml). After treatment with activated carbon, the solution was concentrated to deposit **40s** (7.4 g) as colorless needles.

***trans*-5- and 6-Hydroxymethyl-2-isopropylamino-1,2,3,4-tetrahydronaphthalen-1-ol (29 and 36, Table I)**——$LiAlH_4$ (2 g) was added portionwise to a stirred solution of **7**·HCl (1 g) in tetrahydrofuran (THF, 20 ml) at room temperature and the mixture was stirred for 30 min. Excess $LiAlH_4$ was decomposed with water, inorganic material was filtered off, and the filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was treated with a saturated solution of fumaric acid in ether to give **29**·fumarate (0.6 g) as colorless needles. ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.10—1.30 (6H, m, $CH_3 \times 2$), 4.80 (1H, d, J=7 Hz, C_1–H), 5.0 (2H, s, CH_2–OH), 7.30—7.85 (3H, m, phenyl protons).

The 6-hydroxymethyl isomer (**36**·fumarate, 0.2 g) was obtained as colorless needles from **25** (0.4 g) by the same procedure as that described for the preparation of **29**.

***trans*-5- and 6-Dimethylamino-2-isopropylamino-1,2,3,4-tetrahydronaphthalen-1-ol (30 and 35, Table I)**——The 5-dimethylamino compound (**30**) was prepared from **9**·HCl (1 g) and $LiAlH_4$ (2 g) according to a procedure similar to that used for the preparation of **29**, and isolated as colorless needles of its hydrogen fumarate (0.5 g). The 6-dimethylamino isomer (**35**) was obtained from **19**·HCl (0.8 g) and $LiAlH_4$ (1.6 g) by the same procedure and isolated as colorless needles of its hydrochloride (0.5 g). ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.20—1.40 (6H, m, $CH_3 \times 2$), 3.10 (3H, s, CH_3), 3.15 (3H, s, CH_3), 4.70 (1H, d, J=7 Hz), 3.10—3.60 (3H, m, phenyl protons).

***trans*-6-Amino-5,7-dimethyl-2-(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (31a and 31b, Table I)**——A solution of **13a**·HCl (2.1 g) in MeOH (100 ml) was subjected to catalytic hydrogenolysis over 10% Pd-C (1 g) at room temperature under atmospheric pressure until the absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was concentrated and diluted with AcOEt (100 ml) to precipitate **31a**·HCl (1.4 g). By the same procedure, the 2-(1-methyl-3-phenylpropyl)amino analog (**31b**·HCl) was prepared from **13b**·HCl.

***trans*-5-Alkoxy-6-alkyl-2(*N*-substituted amino)-1,2,3,4-tetrahydronaphthalen-1-ols (32, 33 and 34, Table I)**——Compounds **14b**·HCl, **15**·HCl and **16**·HCl were converted to **32**·HCl, **33**·HCl and **34**·HCl by catalytic hydrogenation in a manner similar to that described for the preparation of **31**. These hydrochlorides were crystallized from MeOH–ether to give colorless prisms.

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17) In the reactions of **41c**, **41j**, **41k** and **41n**, the free bases were used instead of the hydrochlorides. In these cases, a few drops of 20% ethanolic HCl were added to the reaction mixture.

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