[Chem. Pharm. Bull. 25(11)2988—3002(1977)]

UDC 547.655.4.04.09 : 615.217.24.011.5.015.11

Syntheses and β-Adrenoceptor Activities of 2-Alkylamino-6-hydroxy-5-hydroxymethyl-1,2,3,4-tetrahydro-1-naphthalenols

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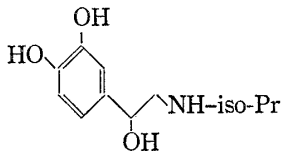
(Received March 22, 1977)

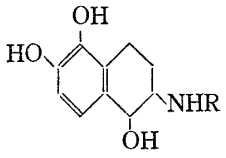
In connection with our earlier studies on β-adrenergic-stimulating activities of ring-closed analogs of β-hydroxycatecholamines, a series of 2-amino- and 2-alkylamino-1,2,3,4-tetrahydro-1-naphthalenols was synthesized with the aim of finding new bronchodilators with minimal cardiovascular side effects. The present paper includes compounds possessing a hydroxy group at the 6-position and a hydroxymethyl, cyano or ureidomethyl group at the 5-position. As starting materials, 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone and methyl 2-hydroxy-1-naphthoate were used. The latter was more advantageous for the synthesis of 5-hydroxymethyl derivatives. Stereoselective reduction of the 1-ketone to give *cis*- or *trans*-2-amino-1-hydroxy compounds was also discussed.

Keywords——Tetrahydronaphthalene; amino alcohol; stereoselective reduction; reductive N-alkylation; 2-alkylamino-1-tetralol; β-adrenoceptor; β_2-stimulant

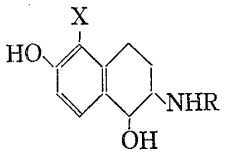
In a previous paper,[2] we reported the synthesis and selective β-adrenoceptor activities of 2-alkylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (A), conformationally fixed analogs of β-hydroxy-catecholamines. Usually catecholamines have activities of short duration because they are rapidly metabolized by catechol O-methyl transferase (COMT). Catecholamines are also inactivated by conversion to the O-sulfates in the intestine; therefore, the activities are greatly reduced upon oral administration. In the case of isoproterenol, replacement of the catechol nucleus by saligenin led to increased duration, β_2-selectivity of the activity and oral efficacy.[3] This prompted us to synthesize 5-hydroxymethyl derivatives of A expecting to obtain a new bronchodilator having improved pharmacological and toxicological properties. Here we report the synthesis of 2-alkylamino-6-hydroxy-5-hydroxymethyl-1,2,3,4-tetrahydro-1-naphthalenols (**1a—1k**) and some 5-cyano and 5-ureidomethyl



isoproterenol



A
R=alkyl



1
X=CH_2OH; CN; $CH_2NHCONH_2$
R=alkyl

Chart 1

1) Location: *Juso-honmachi, Yodogawa-ku, Osaka 532, Japan.*
2) *a*) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, and Y. Sanno, *Life Sci.*, **16**, 305 (1975); *b*) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **25**, 632 (1977); *c*) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), **25**, 2917 (1977).
3) *a*) D. Hartley, D. Jack, L.H.C. Lunts, and A.C. Ritchie, *Nature* (London), **219**, 861 (1968); *b*) R.T. Brittain, J.B. Farmer, D. Jack, L.E. Martin, and W.T. Simpson, *Nature* (London), **219**, 862 (1968); *c*) V.A. Cullum, J.B. Farmer, D. Jack, and G.P. Lavy, *Br. J. Pharmacol.*, **35**, 141 (1969); *d*) D.T. Collin, D. Hartley, D. Jack, L.H.C. Lunts, J.C. Press, A.C. Ritchie, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).

derivatives (**1l**—**1o** and **1p**). Stereoselective synthesis of *cis*- and *trans*-isomers is also described.

Synthesis of 5-Substituted 6-Hydroxy-3,4-dihydro-1(2*H*)-naphthalenones

First, we tried to prepare 5-substituted 6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenones as key intermediates in the synthesis of new tetrahydronaphthalenol adrenoceptor agents (**1a**—**1p**). The chloromethylation of 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**2**) has been reported to occur mainly at the 5-position,[4] however, our reexamination of this reaction showed that the desired chloromethyl derivative was obtained in poor yields mainly because of difficulties in the purification. However, 5-chloromethyl-6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**4**) was isolated almost quantitatively by chloromethylation of 6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**3**), prepared from **2** by demethylation. This 5-chloromethyl derivative (**4**) was unstable under basic conditions and treatment of **4** with benzyl chloride and potassium carbonate failed to give its O-benzyl ether. On the other hand, **4** was easily derived into the 5-methoxymethyl compound (**5**) using a base (triethylamine) in methanol, *via* a quinonemethide intermediate.[5] The product (**5**) was stable in basic medium

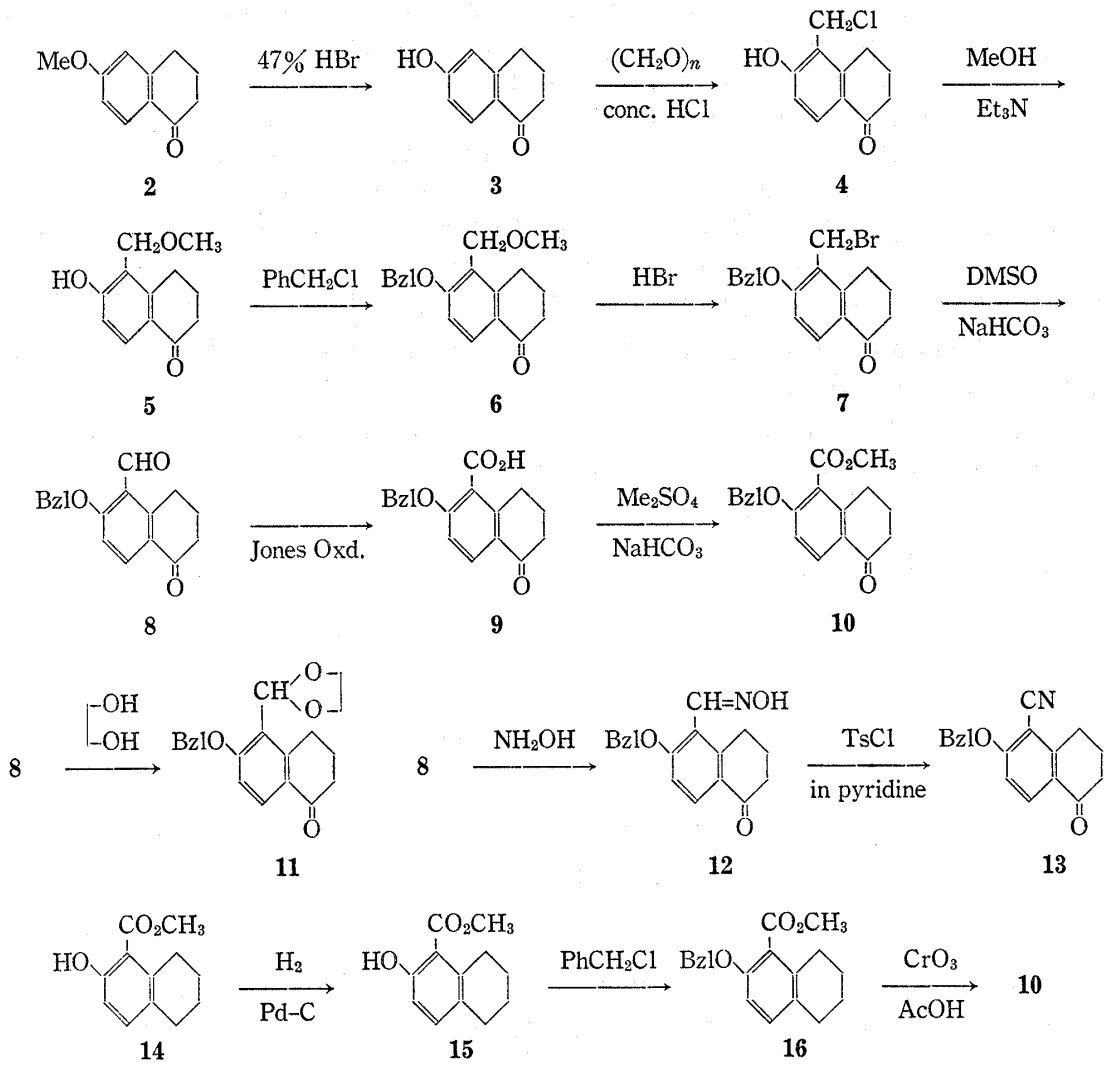


Chart 2

4) M.M.J. Delobell, M. Fetizon, and G. Moreau, *C.R. Acad. Sci.*, **251**, 1136 (1960).
5) A.B. Turner, *Quart. Rev.*, **18**, 347 (1964).

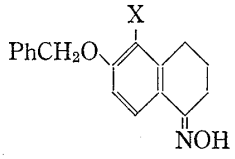
and O-benzylated by benzyl chloride and potassium carbonate in dimethylformamide (DMF), yielding 6-benzyloxy-5-methoxymethyl-3,4-dihydro-1(2*H*)-naphthalenone (**6**). The methoxy group of **6** was then replaced with a bromine atom by treatment with a slight excess of 47% hydrobromic acid in acetic acid at 40—50°. The resulting 5-bromomethyl derivative (**7**) was oxidized in a dimethylsulfoxide-sodium bicarbonate system, affording the aldehyde (**8**) and the 5-hydroxymethyl derivative as a small amount of by-product. Jones oxidation of **8** gave the carboxylic acid (**9**) and subsequent esterification gave the methyl ester (**10**) in good yield. The aldehyde ethylene acetal (**11**) was prepared by condensation of **8** and ethylene glycol under refluxing in benzene containing *p*-toluenesulfonic acid as a catalyst. Treatment of **8** with an equimolecular amount of hydroxylamine gave the aldoxime (**12**). Dehydration of **12** with benzenesulfonyl chloride in pyridine afforded the 5-cyano derivative (**13**).

As an alternative practical method for preparing 5-methoxycarbonyl derivative (**10**), we examined a synthetic route from methyl 2-hydroxy-1-naphthoate (**14**). Arnold and his co-workers have reported that hydrogenation of methyl 3-hydroxy-2-naphthoate in the presence of Raney nickel quantitatively gives methyl 3-hydroxy-5,6,7,8-tetrahydro-2-naphthoate.[6] When methyl 2-hydroxy-1-naphthoate (**14**) was hydrogenated under similar conditions, the product was a mixture of methyl 2-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (**15**, *ca.* 10—20%) and methyl 2-hydroxy-1,2,3,4-tetrahydro-1-naphthoate (80—90%), whose structures were deduced from the nuclear magnetic resonance (NMR) spectrum of the reaction mixture. But hydrogenation of **14** using palladium charcoal as a catalyst mainly gave the desired product (**15**, *ca.* 70%). The crude reaction product was O-benzylated and recrystallized from methanol to give the pure O-benzyl ether (**16**). Oxidation of **16** was successively carried out with chromic anhydride in an acetic acid solution, giving a tetralone derivative. This compound was collaborated to be identical with **10**, which had been derived from 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**2**), by infrared (IR) and NMR spectra.

Synthesis of 5-Substituted 2-Alkylamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols from 3,4-Dihydro-1(2*H*)-naphthalenones

To prepare 2-alkylamino derivatives, we attempted a substitution reaction at the 2-position of 2-bromo-3,4-dihydro-1(2*H*)-naphthalenone with alkylamine. Bromination of **10** and **13** by pyridine hydrobromide perbromide in acetic acid gave α-bromo-tetralins **18** and **17**

TABLE I. 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oximes (**25**—**28**)

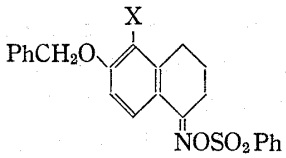


Compd.	X	Yield (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
25	CO_2CH_3	72	186—187	EtOH	$C_{19}H_{19}NO_4$	70.14 (69.89)	5.89 (5.87)	4.31 (4.05)
26	CHO	66	176—177	Benzene–*n*-hexane	$C_{18}H_{17}NO_3$	73.20 (73.21)	5.80 (5.75)	4.74 (4.75)
27	C=NOH	85	162—164	Benzene–AcOEt	$C_{18}H_{18}N_2O_3$	69.66 (69.53)	5.85 (5.75)	9.03 (9.01)
28	CH_2OCH_3	95	138—140	EtOH	$C_{19}H_{21}NO_3$	73.29 (72.90)	6.80 (6.61)	4.50 (4.32)

6) R.T. Arnold, H.E. Zaugg, and J. Sprung, *J. Am. Chem. Soc.*, **63**, 1314 (1941).

respectively, in good yields. However, none of the replacement reactions of **17** or **18** with various alkylamines proceeded successfully. Only N-methylbenzylamine when employed as a nucleophile gave **19** as a good crystalline solid from **17**. Thin-layer chromatography

Table II. 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime O-Benzenesulfonates (**29**—**32**)



Compd.	X	Yield (%)	mp (°C)	Recrystallization solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
29	CO_2CH_3	86	146—147	Benzene–*n*-hexane	$C_{25}H_{23}NO_6S$	64.50 (64.74)	4.98 (5.06)	3.01 (2.81)
30	CHO	80	142—143	Benzene–cyclohexane	$C_{24}H_{21}NO_5S$	66.19 (66.41)	4.86 (4.78)	3.32 (3.41)
31	CN	77	161—163	Benzene	$C_{24}H_{20}N_2O_4S$	66.65 (66.53)	4.66 (4.40)	6.48 (6.47)
32	CH_2OCH_3	78	Oil		$C_{25}H_{25}NO_5S$	66.50 (66.31)	5.58 (5.20)	3.10 (2.98)

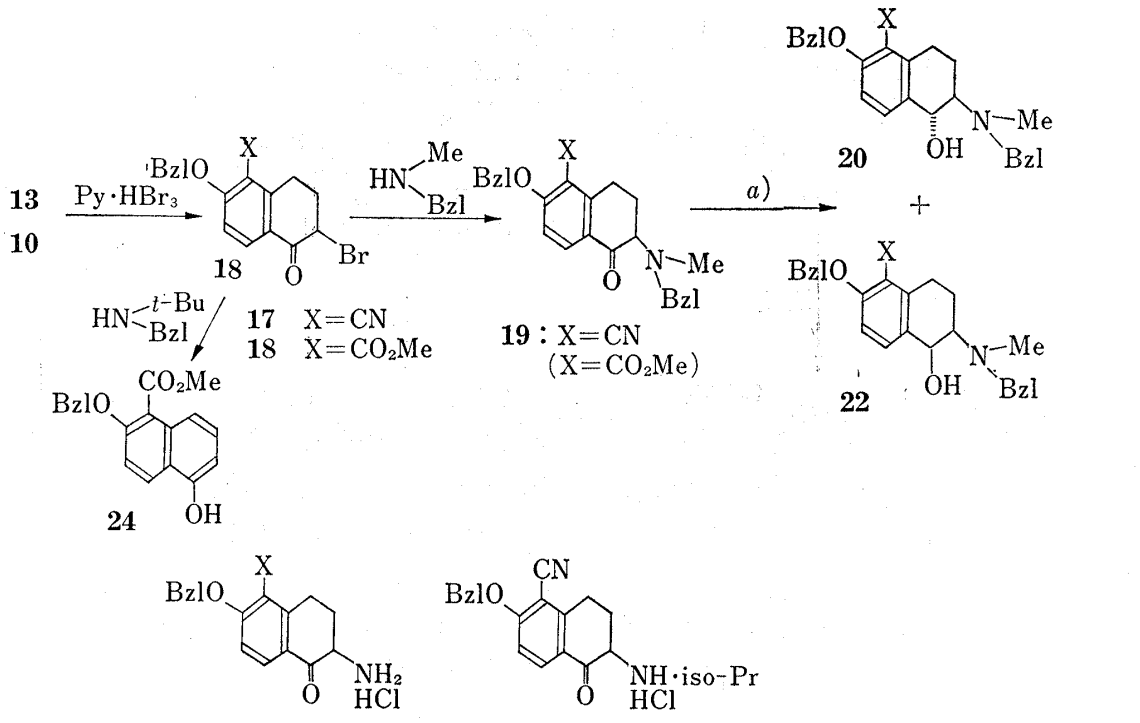


Chart 3

(TLC) of the reaction products between **18** and isopropylamine, *tert*-butylamine or N-*tert*-butylbenzylamine showed that the reaction was complicated giving various products. The isolable product common to these reactions was methyl 2-benzyloxy-5-hydroxy-1-naphthoate (**24**). These results suggest that the S_N2 reaction of **17** and **18** with amines is strongly affected by the basicity and bulkiness of the reactant and proceeds competitively with the E_2 reaction. Reduction of the N-methylbenzyl derivative (**19**) with sodium borohydride afforded a mixture of *trans*- and *cis*-amino alcohols in a ratio of 3:1. Each isomer was isolated by column chromatography on silica gel and the structure was determined on the basis of the typical coupling constants of the methine proton at the C_1-position (>C<u>H</u>–OH) in the NMR spectra. The *trans*-isomer (**20**) has a doublet at 4.55 ppm (J=10Hz), while the *cis*-isomer (**22**) has a doublet at 4.71 ppm (J=3 Hz). When **19** was reduced with more bulky lithium tri-*tert*-butoxyaluminum hydride, the *cis*-isomer became the main product; the ratio of **20** to **22** was 1:2. The stereoselectivity on reduction of 3,4-dihydro-1(2*H*)-naphthalenones having a bulky amino group at the 2-position may be affected by steric interaction on accessibility of the reagent to the carbonyl carbon (kinetic control).

To introduce other alkylamino groups to the 2-position, the following processes were examined. 3,4-Dihydro-1(2*H*)-naphthalenones (**6**, **10**, **11**) were converted into oximes (**25**—**28**) by the conventional method (Table I). Oximation of 5-aldehyde ethylene acetal (**11**) even with an equimolecular amount of hydroxylamine hydrochloride in pyridine produced a considerable amount of the dioxime (**27**). Hydrolysis of the reaction mixture followed by chromatographic separation afforded **26** and **27**. Compound **26** was preferably formed by oximation of **11** with hydroxylamine base in ethanolic solution and subsequent hydrolysis.

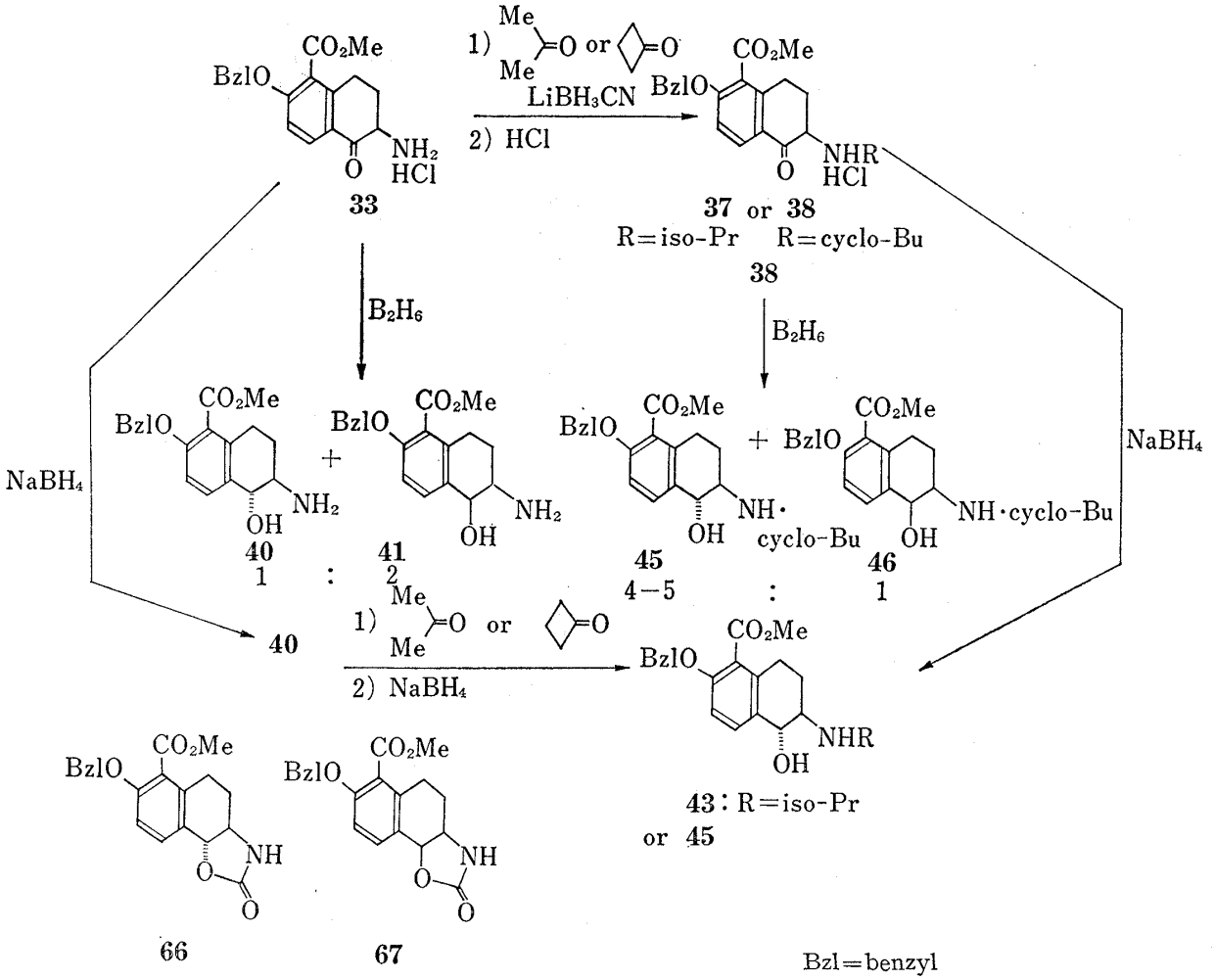
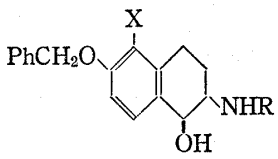
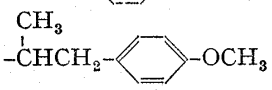
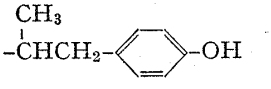
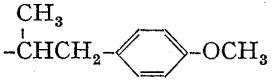
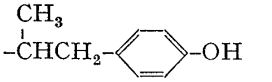


Chart 4

TABLE III. 5-Substituted 2-Amino- and 2-Alkylamino- 6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenols (**40—65**)



Compd.	X	R	Configuration at 1-position	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
40	CO_2CH_3	H	*trans*	78	124—126	$C_{19}H_{21}NO_4$	69.70 (69.52)	6.47 (6.38)	4.28 (4.21)
40-HCl	CO_2CH_3	H	*trans*	—	215—216[a]	$C_{19}H_{22}ClNO_4$	62.72 (62.53)	6.09 (6.22)	3.85 (3.89)
41	CO_2CH_3	H	*cis*	—	140—142	$C_{19}H_{21}NO_4$	69.70 (69.79)	6.47 (6.41)	4.28 (4.33)
41-HCl	CO_2CH_3	H	*cis*	38	220—222[a]	$C_{19}H_{22}ClNO_4$	62.72 (62.57)	6.09 (5.90)	3.85 (3.65)
42	CN	H	*trans*	82	272—276[a]	$C_{18}H_{19}ClNO_2$	65.35 (65.24)	5.79 (5.47)	8.47 (8.32)
43	CO_2CH_3	iso-C_3H_7	*trans*	85	91—92	$C_{22}H_{27}NO_4$	71.52 (71.31)	7.37 (7.51)	3.79 (3.65)
43-HCl	CO_2CH_3	iso-C_3H_7	*trans*	—	247—249[a]	$C_{22}H_{28}ClNO_4$	65.09 (65.24)	6.95 (7.03)	3.45 (3.30)
44	CO_2CH_3	iso-C_3H_7	*cis*	84	113—114	$C_{22}H_{27}NO_4$	71.52 (71.89)	7.37 (7.34)	3.79 (3.47)
44-HCl	CO_2CH_3	iso-C_3H_7	*cis*	—	267—270[a]	$C_{22}H_{28}ClNO_4$	65.09 (64.90)	6.95 (6.94)	3.45 (3.41)
45	CO_2CH_3		*trans*	75	117—119	$C_{23}H_{27}NO_4$	72.42 (72.16)	7.13 (7.08)	3.67 (3.65)
45-HCl	CO_2CH_3		*trans*	—	205—208[a]	$C_{23}H_{28}ClNO_4$	66.10 (66.07)	6.75 (6.55)	3.35 (3.31)
46	CO_2CH_3		*cis*	78	115—116	$C_{23}H_{27}NO_4$	72.42 (72.47)	7.13 (6.85)	3.67 (3.52)
46-HCl	CO_2CH_3		*cis*	—	254—257[a]	$C_{23}H_{28}ClNO_4$	66.10 (66.00)	6.75 (6.59)	3.35 (3.40)
47	CN	iso-C_3H_7	*trans*	85	141—143	$C_{21}H_{24}N_2O_2 \cdot 1/2H_2O$	73.02 (72.89)	7.30 (7.38)	8.11 (8.38)
48	CO_2CH_3		*trans*	63	102—104	$C_{24}H_{24}NO_4$	72.88 (72.76)	7.39 (7.38)	3.54 (3.46)
49	CO_2CH_3		*trans*	59	111—113	$C_{25}H_{31}NO_4$	73.32 (73.18)	7.63 (7.52)	3.42 (3.32)
50	CO_2CH_3		*trans*	56	84—86	$C_{29}H_{33}NO_5$	73.24 (73.03)	6.99 (7.00)	2.95 (2.97)
51	CO_2CH_3		*trans*	50	182—192[a]	$C_{28}H_{32}ClNO_5$	67.53 (67.10)	6.48 (6.26)	2.81 (2.81)
52	CO_2CH_3	$CO_2C_2H_5$	*trans*	78	147—148	$C_{22}H_{25}NO_6$	66.15 (66.12)	6.31 (6.26)	3.51 (3.45)
54	CH_2OH	H	*trans*	29	148—150	$C_{18}H_{21}NO_3 \cdot 1/2H_2O$	70.11 (70.38)	7.19 (7.23)	4.54 (4.79)
55	CH_2OH	CH_3	*trans*	55	172—173	$C_{19}H_{23}NO_3 \cdot 2/3H_2O$	70.13 (69.86)	7.54 (7.25)	4.30 (4.16)
56	CH_2OH	C_2H_5	*trans*	60	158—159	$C_{20}H_{25}NO_3$	73.36 (73.34)	7.70 (7.80)	4.28 (4.05)
57	CH_2OH	iso-C_3H_7	*trans*	85	142—144	$C_{21}H_{27}NO_3$	73.87 (73.68)	7.97 (7.74)	4.10 (4.05)
57-HCl	CH_2OH	iso-C_3H_7	*trans*	—	236—237[a]	$C_{21}H_{28}ClNO_3 \cdot 1/2H_2O$	65.19 (65.39)	7.55 (7.38)	3.62 (3.74)
58	CH_2OH	iso-C_3H_7	*cis*	56	131—133	$C_{21}H_{27}NO_3$	73.87 (73.53)	7.97 (8.04)	4.10 (3.99)

Compd.	X	R	Configuration at 1-position	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
58-HCl	CH_2OH	iso-C_3H_7	*cis*	—	212—214[a]	$C_{21}H_{28}ClNO_3$	66.74 (66.69)	7.47 (7.54)	3.71 (3.85)
59	CH_2OH		*trans*	76	156—158	$C_{22}H_{27}NO_3$	74.75 (74.46)	7.70 (7.75)	3.96 (3.82)
59-HCl	CH_2OH		*trans*	—	206—208[a]	$C_{22}H_{28}ClNO_3$	67.77 (67.61)	7.24 (7.30)	3.59 (3.64)
60	CH_2OH		*cis*	53	165—166	$C_{22}H_{27}NO_3$	74.75 (74.47)	7.70 (7.65)	3.96 (4.02)
60-HCl	CH_2OH		*cis*	—	209—211[a]	$C_{22}H_{28}ClNO_3$	67.77 (67.65)	7.24 (7.35)	3.59 (3.75)
61	CH_2OH		*trans*	83	128—130	$C_{23}H_{29}NO_3$	75.17 (75.30)	7.95 (8.01)	3.81 (3.94)
62	CH_2OH		*trans*	85	145—147	$C_{24}H_{31}NO_3$	75.56 (75.46)	8.19 (8.20)	3.67 (3.56)
63	CH_2OH		*trans*	65	119—125	$C_{30}H_{37}NO_6$	70.98 (70.77)	7.35 (7.41)	2.76 (2.51)
64	CH_2OH		*trans*	77	175—178	NMR (DMSO-d_6) δ: 4.66 (1H, d, J=9Hz, 1-H)			
65	$CH_2NHCONH_2$	iso-C_3H_7	*trans*	51	202—204	$C_{22}H_{29}N_3O_3$	68.90 (68.72)	7.62 (7.81)	10.96 (11.23)

a) Hydrochloride decomposition.

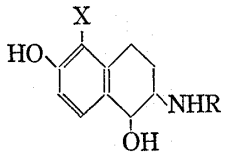
Treatment of the oximes (**25**—**28**) with benzenesulfonyl chloride in pyridine gave oxime O-benzenesulfonates (**29**—**32**) (Table II). On sulfonylation of **12**, the aldoxime group was converted into a cyano group. Neber rearrangement of **29**—**32** was carried out using potassium ethoxide and subsequent treatment with hydrochloric acid yielded 2-amino-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride (**33**—**36**). 5-Formyl and 5-methoxymethyl derivatives (**34** and **36**) were obtained in poor yields by these rearrangements. The 5-methoxymethyl moiety was partly converted into the chloromethyl group during post-treatment with hydrochloric acid. Therefore, the route through methoxycarbonyl and 5-cyano derivatives (**33** and **35**) seemed to be the most promising for further studies. Reduction of **33** with sodium borohydride in ethanol yielded the *trans*-amino alcohol (**40**) exclusively. Similarly, *trans*-isopropylamino and *trans*-cyclobutylamino alcohols (**43** and **45**) were synthesized by stereoselective reduction of the corresponding 2-alkylamino-3,4-dihydro-1(2*H*)-naphthalenone derivatives (**37** and **38**), which were synthesized from **33** by N-alkylation using lithium cyanoborohydride[7] as a reductive alkylating agent with carbonyl compounds. In contrast to the reduction of **33** with sodium borohydride, reduction with diborane in tetrahydrofuran afforded the *cis*-amino alcohol (**41**) as the main product (**40**: **41**=1: 2). Recrystallization from methanol gave pure **41**. The stereoselectivity of this reaction may be explained in terms of affinity of the boron atom of diborane for the nitrogen and oxygen atoms at the 2- and 1-positions, respectively, in the tetralin ring. Marked decrease in the ratio of the *cis*-isomer (**46**) on reduction of the N-cyclobutyl derivative (**38**) showed that this stereoselectivity might be sensitive to steric hindrance.

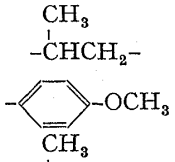
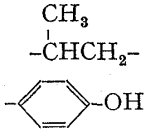
7) *a*) R.F. Borch and H.D. Durst, *J. Am. Chem. Soc.*, **91**, 3996 (1969); *b*) R.F. Borch, M.D. Bernstein, and H.D. Durst, *ibid.*, **93**, 2897 (1971).

8) Although another set of diastereoisomers will exist in compounds **50** and **51**, in which the substituent R involves an asymmetric center on reductive alkylation, we have no evidence at present as to whether the isolated compounds correspond to one diastereoisomer or mixtures of the two isomers with respect to the asymmetric carbon in R.

Reductive N-alkylation of **40** with various carbonyl compounds using lithium cyanoborohydride in methanol, gave **43**—**51**.[8] Alternatively, both *trans*- and *cis*-amino tetralols (**40** and **41**) were N-alkylated in good yields to give **43**—**46** when they were first heated with acetone or cyclobutanone in benzene and subsequently reduced with sodium borohydride. Treatment of **40** with ethyl chloroformate gave the ethoxycarbonylamino derivative (**52**) in good yield, whereas acetylation of **40** in pyridine yielded the diacetylated derivative (**53**). The methoxycarbonyl group of **43**—**46** and **48**—**53** was converted into a hydroxymethyl group by reduction with lithium aluminum hydride in tetrahydrofuran. In the case of **52** or **53**,

Table IV. 5-Substituted 2-Amino- and 2-Alkylamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1a**—**1p**)



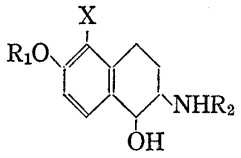
Compd.	X	R	Salt	Configuration at 1-position	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
1a	CH_2OH	H	*p*-Anisic acid	*trans*	42	120—123	$C_{19}H_{23}N_6O \cdot H_2O$	60.15 (59.92)	6.42 (6.26)	3.69 (3.92)
1b	CH_2OH	CH_3	base	*trans*	88	198—210	$C_{12}H_{17}NO_3 \cdot 1/2H_2O$	62.05 (61.75)	7.81 (7.75)	6.03 (5.75)
1c	CH_2OH	C_2H_5	AcOH	*trans*	70	177—180	$C_{15}H_{23}NO_5$	60.59 (60.26)	7.80 (7.88)	4.71 (4.71)
1d	CH_2OH	iso-C_3H_7	HCl	*trans*	85	205—210	$C_{14}H_{22}ClNO_3 \cdot 3/2H_2O$	53.41 (53.50)	8.00 (8.44)	4.45 (4.42)
1e	CH_2OH	iso-C_3H_7	HCl	*cis*	72	223—230	$C_{14}H_{22}ClNO_3$	58.43 (58.44)	7.71 (7.88)	4.87 (4.90)
1f	CH_2OH		HCl	*trans*	75	210—230	$C_{15}H_{22}ClNO_3$	60.09 (59.86)	7.40 (7.48)	4.67 (4.72)
1g	CH_2OH		HCl	*cis*	70	203—217	$C_{15}H_{22}ClNO_3$	60.09 (59.86)	7.40 (7.48)	4.67 (4.72)
1h	CH_2OH		AcOH	*trans*	72	145—148	$C_{18}H_{27}NO_5 \cdot 1/3H_2O$	63.14 (63.31)	8.34 (8.34)	4.09 (3.89)
1i	CH_2OH		AcOH	*trans*	88	135—137	$C_{19}H_{29}NO_5 \cdot H_2O$	61.77 (61.56)	8.46 (8.69)	3.79 (3.61)
1j	CH_2OH		AcOH	*trans*	61	146—148	NMR (DMSO-d_6-D_2O) δ: 4.42 (1H, d, J=8Hz, 1-H)			
1k	CH_2OH		base	*trans*	71	135—137	NMR (DMSO-d_6-D_2O) δ: 4.78 (1H, d, J=9Hz, 1-H)			
1l	CN	H	HCl	*trans*	93	259—261	$C_{11}H_{13}ClN_2O_2 \cdot 1/4H_2O$	53.88 (53.68)	5.55 (5.25)	11.43 (10.91)
1m	CN	CH_3	HCl	*trans*	73	230—232	$C_{12}H_{15}ClN_2O_2$	56.58 (56.13)	5.94 (5.95)	11.00 (10.92)
1n	CN	CH_3	HCl	*cis*	77	226—227	$C_{12}H_{15}ClN_2O_2$	56.58 (56.30)	5.94 (6.09)	11.00 (10.88)
1o	CN	iso-C_3H_7	base	*trans*	77	183—185	$C_{14}H_{18}N_2O_2 \cdot 1/2H_2O$	65.86 (65.94)	7.50 (7.42)	10.91 (10.54)
1p	CH_2NH-$CONH_2$	iso-C_3H_7	base	*trans*	56	120—122	$C_{15}H_{23}N_3O_3$	61.41 (61.31)	7.90 (7.78)	14.33 (14.01)

a) Decomposition.

the N-ethoxycarbonyl or N-acethyl group, respectively, was simultaneously reduced to afford the 2-methylamino (**55**) or the 2-ethylamino (**56**) derivative. The 5-ureidomethyl compound (**65**) was synthesized by reaction of the crude aminomethyl compound, derived by lithium aluminum hydride reduction of the corresponding 5-cyano derivative (**47**) with isocyanic acid in methanol. Table III summarizes the physical properties of 5-substituted 2-alkylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenols (**40**—**65**). Finaly, removal of the benzyl group, a group protecting hydroxy function at the 6-position, was accomplished by catalytic hydrogenation in methanol using 5% palladium charcoal under atmospheric pressure at room temperature. Table IV gives the yields of the 5-substituted 2-amino- and 2-alkylamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1a**—**1p**) and their physical properties.

The most stable conformation of the hydrogenated ring in tetralin derivatives has been considered to the half-chair form[9] in which a pair of *trans*-substituents at the 1- and 2-position are diaxial or diequatorial and *cis*-substituents are axial- equatorial or equatorial-axial. Chemical shifts and coupling constants of the C_1-position (>C<u>H</u>–OH) and C_1-hydroxy proton (>CH–O<u>H</u>) in NMR spectra of *cis*- and *trans*-2-amino- and 2-alkylamino-1,2,3,4-tetrahydro-1-naphthalenols are shown in Table V. Each *trans*-isomer has a peak of C_1-proton at higher field as well as a larger coupling constant than the corresponding *cis*-isomer. These values show that the *trans*-isomer has diequatorial 1-hydroxy and 2-amino groups in its half-chair conformation and the *cis*-isomer may have axial 1-hydroxy and equatorial 2-amino groups. This conformation is supported by NMR study of hydroxy proton of epimeric alcohols in

Table V. NMR Spectral Data of C_1-Protons and Hydroxy Protons in *cis*- and *trans*-Isomers of 2-Amino- and 2-Alkylamino-1,2,3,4-tetrahydro-1-naphthalenols



R_1	R_2	X	Chemical shift, ppm (Coupling constant, Hz)					
			cis-Isomer			*trans*-Isomer		
			Base	HCl Salt		Base	HCl salt	
			C_1<u>H</u>-OH	C_1<u>H</u>-OH[b]	C_1H-O<u>H</u>[c]	C_1<u>H</u>-OH	C_1<u>H</u>-OH[b]	C_1H-O<u>H</u>[c]
Bzl	H	CO_2CH_3	4.36[a] (3)	4.76 (3)	5.93 (6.0)	4.08[a] (8)	4.60 (8)	6.20 (7.0)
Bzl	iso-Pr	CO_2CH_3	4.49[a] (3)	4.76 (3)	6.05 (5.5)	4.22[a] (8)	4.68 (8)	6.17 (6.0)
Bzl	cyclo-Bu	CO_2CH_3	4.48[a] (3)	4.72 (3)	6.00 (5.0)	4.26[a] (8)	4.65 (8)	6.15 (6.0)
Bzl	iso-Pr	CH_2OH	4.46[c] (3)	4.81 (3)	6.07 (5.0)	4.23[c] (8)	4.76 (8)	—
Bzl	cyclo-Bu	CH_2OH	4.43[c] (3)	4.72 (3)	5.92 (5.5)	4.14[c] (7)	4.67 (8)	6.03 (7.0)
H	iso-Pr	CH_2OH	—	4.76 (3)	5.88 (broad)	4.12[c] (7)	4.77 (9)	5.88 (7.5)
H	cyclo-Bu	CH_2OH	—	4.69 (3)	5.83 (5.0)	—	4.63 (8)	5.91 (7.0)

a) In $CDCl_3$ solution. *b*) In DMSO-d_6-D_2O solution. *c*) In DMSO-d_6 solution.

9) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," John Wiley and Sons Inc., New York, N.Y., 1965, p. 109.

10) *a*) C.P. Rader, *J. Am. Chem. Soc.*, **88**, 1713 (1966); *b*) R.K. Sehgal, R.U. Koenigsberger, and T.J. Howard, *Tetrahedron Lett.*, **1974**, 4173.

dimethylsulfoxide, and the method is useful for determining the stereochemistry.[10] Each H–C_1–OH coupling constant in the *trans*-amino alcohols is larger than and each peak of the hydroxy protons of *trans*-amino alcohols is at higher field than that of the corresponding *cis*-isomer. Ring-closed oxazolidin-2-one derivatives (**66** and **67**) from the reaction of *trans*- and *cis*-amino alcohols (**40** and **41**) with phosgen also had different NMR spectra. However, the value of the coupling constant of the C_1-proton in the tetralin ring (–CH(OH)–CH(NH)–) of the *trans*-isomer was larger than that of the *cis*-isomer. This inconsistency with the results of normal oxazolidin-2-one derivatives[11] may be attributed to a distorted conformation of the oxazolidinone ring in **66** and **67** due to the steric strain caused by the cyclohexene ring of the tetraline skeleton directly attached to the oxazolidinone.

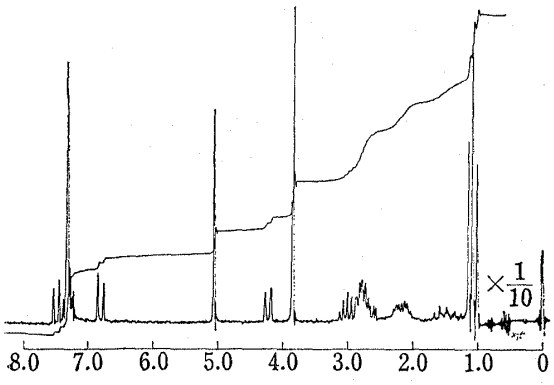


Fig. 1. NMR Spectrum of **43**(*trans*-isomer) in $CDCl_3$ (100 MHz)

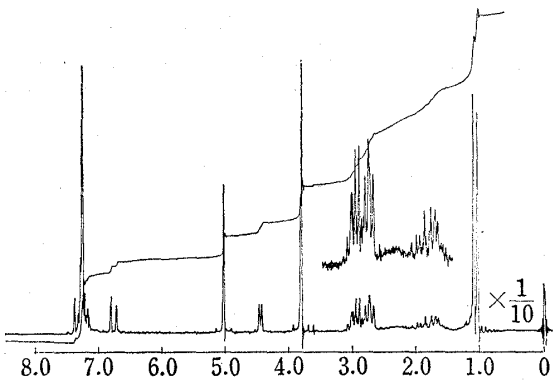


Fig. 2. NMR Spectrum of **44** (*cis*-isomer) in $CDCl_3$ (100 MHz)

TABLE VI. β-Adrenoceptor Activity of 2-Alkylamino-6-hydroxy-5-hydroxymethyl-1,2,3,4-tetrahydro-1-naphthalenols

	Compound	β_1[a]				β_2[b]				Selectivity	
		n	pD_2	*i.a.*[c]	Ratio[d]	*n*	pD_2	*i.a.*[c]	Ratio[d]	β_1/β_2	Ratio[d]
1[e]	*l*-Isoproterenol[f]	39	8.42±0.04	1.0	1.0	41	8.02±0.04	1.0	1.0	0.40	1.0
	dl-Salbutamol[g]	9	6.56±0.08	0.8	0.014	11	7.77±0.12	1.0	0.56	16.3	40
	Metaproterenol[h]	4	6.63±0.05	1.0	0.032	2	6.75	1.0	0.086	1.32	3.3
	1d	8	6.56±0.04	1.0	0.014	12	8.04±0.10	1.0	1.10	30.2	75.5
	1f	9	7.06±0.11	1.0	0.044	5	8.48±0.17	1.0	2.89	26.3	66
2[e]	*l*-Isoproterenol	19	8.88±0.05	1.0	1.0	22	8.79±0.06	1.0	1.0	0.8	1.0
	1c	3	6.19±0.12	0.81	0.002	3	8.18±0.19	1.0	0.246	97	120
	1g	4	5.11±0.09	0.50	0.0002	4	6.90±0.15	1.0	0.013	62	76
	1h	3	6.39±0.09	0.79	0.003	3	8.16±0.04	1.0	0.235	59	74
	1j	3	7.73±0.08	0.88	0.071	3	8.93±0.09	1.0	1.38	16	20
	1k	4	8.27±0.09	0.94	0.246	4	9.57±0.10	1.0	6.03	20	25

a) Positive chronotropic action in isolated guinea-pig atria.
b) Relaxing action in isolated guinea-pig tracheal chain.
c) Intrinsic activity.
d) *l*-Isoproterenol=1.0.
e) The experimental 1 and 2 were carried out in different seasons.
f) Proterenol®, Nikken Chemical Co., Ltd..
g) Synthesized in our laboratories.
h) Alotec®, Tanabe Seiyaku Co., Ltd.

11) S.L. Spassov, J.N. Stefanovsky, B.J. Kurter, and G. Forder, *Chem. Ber.* **105**, 2426 (1972).

Pharmacological Activities

5-Substituted 2-alkylamino-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenols synthesized in this paper were evaluated *in vitro* for their ability to relax guinea-pig tracheal strips partially contracted with potassium ion (β_2-stimulating activity) and to increase spontaneously beating rate of isolated guinea-pig atria (β_1-stimulating activity).[12] Potencies of tested compounds were expressed as negative log molar ED_{50} values (pD_2). Intrinsic activities[13] were derived by dividing the maximum response to the compound by the maximum *l*-isoproterenol-induced response. The selectivity of the compound for β_2-adrenoceptor is shown as the molar ratio of ED_{50} values for tracheo-bronchial *vs.* cardiac muscle. Table VI shows some of the results.

5-Hydroxymethyl derivatives showed β_2-stimulating action and progressive selectivity for the bronchial muscle. The effects of alkyl or cycloalkyl substituents at the 2-amino group on β_2-stimulating activity increased in the following order: cyclopentyl<ethyl<isopropyl<cyclobutyl. *p*-Hydroxy- or *p*-methoxyphenyl-isopropyl derivatives (**1k** and **1j**) showed potent β_2-stimulating activities. From the stereochemical point of view, the *trans*-isomer showed more potent bronchorelaxing activity than the corresponding *cis*-isomer. Further pharmacological evaluation of these compounds as new β_2-selective bronchodilators is in progress.

Experimental[14]

5-Chloromethyl-6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (4)——To a mixture of 6-hydroxy-3,4-dihydro-1(2*H*)-naphthalenone (3, 20 g)[15] and conc. HCl (110 ml) was added paraformaldehyde (4.6 g) and the mixture was stirred at room temperature for 20 hr. Next, water (200 ml) was added. The resulting precipitate was collected by filtration, washed with water and hot benzene, and dried to give 4 (21 g, 81%) as pale reddish crystals. mp 172—174° (dec.). IR ν_{max}^{KBr} cm^{-1}: 3300—3000 (OH), 1640 (C=O). NMR (DMSO-d_6) δ: 4.80 (2H, s, CH_2Cl), 6.88 (1H, d, J=8 Hz, 7-H), 7.83 (1H, d, J=8 Hz, 8-H). *Anal.* Calcd. for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.66; H, 5.13.

6-Hydroxy-5-methoxymethyl-3,4-dihydro-1(2*H*)-naphthalenone (5)——To a solution of 4 (21 g) in MeOH (300 ml) was added triethylamine (17 ml). The reaction mixture was refluxed for 3 hr and then evaporated to dryness *in vacuo*. The residue was dissolved in AcOEt (500 ml) then AcOH (5 ml) was added. The mixture was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from benzene–*n*-hexane, yielding 5 (19 g, 92%) as colorless prisms, mp 142—143°. IR ν_{max}^{KBr} cm^{-1}: 3100 (OH), 1630 (C=O). NMR ($CDCl_3$) δ: 3.27 (3H, s, OCH_3), 4.50 (2H, s, $-CH_2O-$). *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.82. Found: C, 69.87; H, 6.82.

6-Benzyloxy-5-methoxymethyl-3,4-dihydro-1(2*H*)-naphthalenone (6)——A mixture of 5 (52 g), benzyl chloride (32 g) and anhydrous K_2CO_3 (35 g) in DMF (300 ml) was stirred at 80—100° for 4 hr. The reaction mixture was poured into ice-water (1 l). The resulting precipitate was collected by filtration, washed with water and recrystallized from *n*-hexane, giving 6 (58 g, 78%) as colorless needles, mp 55—56°. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O). NMR ($CDCl_3$) δ: 3.35 (3H, s, OCH_3), 4.61 (2H, s, CH_2O-), 5.16 (2H, s, $PhCH_2O$). *Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.75; H, 6.83.

6-Benzyloxy-5-bromomethyl-3,4-dihydro-1(2*H*)-naphthalenone (7)——To a solution of 6 (58 g) in AcOH (200 ml) was added 47% aqueous HBr (34 ml). The mixture was warmed at 45—50° for 4 hr and evaporated *in vacuo*. The residue was dissolved in benzene (500 ml) and the solution was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from cyclohexane to give 7 (59 g, 89%) as colorless needles, mp 103—104°. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O). NMR ($CDCl_3$) δ: 4.63 (2H, s, CH_2Br), 5.26 (2H, s, $PhCH_2O-$), 6.85 (1H, d, J=10 Hz, 7-H), 8.01 (1H, d, J=10 Hz, 8-H). *Anal.* Calcd. for $C_{18}H_{17}BrO_3$: C, 62.62; H, 4.96. Found: C, 62.23; H, 4.96.

Oxidation of 7 with Dimethylsulfoxide-Sodium Bicarbonate——To a suspension of $NaHCO_3$ (80 g) in

12) Detailed procedures were reported in ref. 2).
13) E.J. Ariens, A.M. Simonis, and J.M. Van Rossum, "Molecular Pharmacology," Vol. 1, E.J. Ariens, Ed., Academic Press, New York, N.Y., 1964, p. 171.
14) All melting points were determined with a Yanagimoto Micro Melting Point apparatus (microscope hot stage) and are uncorrected. IR spectra were measured with a Hitachi Model 215 infrated spectrophotometer. NMR spectra were determined with a Varian Model HA-100 spectrophotometer using tetramethylsilane as an internal standard. Mass spectra were taken with a JEOL JMS-01SC spectrometer.
15) G. Haberland, *Chem. Ber.*, **69**, 1380 (1936).

DMSO (400 ml) freshly distilled from CaH_2, **7** (44 g) was added with stirring under N_2 atmosphere. The reaction mixture was stirred at 100° for a further 20 min and poured into ice-water. The resulting precipitate was collected by filtration, washed with water and recrystallized from MeOH to give 2-benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthalenecarbaldehyde (**8**) as colorless needles (23 g, 64%), mp 97—98°. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). NMR ($CDCl_3$) δ: 10.80 (1H, s, CHO). *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.22; H, 5.71. The mother liquor was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$ as eluant to give 6-benzyloxy-5-hydroxymethyl-3,4-dihydro-1(2*H*)-naphthalenone (2.4 g, 6.5%), mp 114—115° (benzene–*n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1650 (C=O). NMR ($CDCl_3$) δ: 4.79 (2H, s, CH_2OH). *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.32. Found: C, 76.53; H, 6.28.

2-Benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthoic Acid (**9**)——To a solution of **8** (3.0 g) in acetone (50 ml), Jones reagent (5 ml) was added dropwise under stirring at room temperature. After stirring for 1 hr, the excess reagent was decomposed with MeOH. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue dissolved in AcOEt (100 ml) was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from acetone to give **9** (2.3 g, 73%) as colorless prisms, mp 221—223°. IR ν_{max}^{KBr} cm^{-1}: 3200—2500 (COOH), 1630 (COOH). *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.76; H, 5.40.

Methyl 2-Benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthoate (**10**)——A mixture of **9** (6.0 g), dimethylsulfate (3.0 g), anhydrous K_2CO_3 (4.0 g) in acetone (50 ml) was refluxed for 2 hr. After cooling, the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Benzene and water were added to the residue, then the mixture was shaken vigorously. The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from ether–*n*-hexane to afford **10** (5.2 g, 83%) as colorless prisms, mp 55—56°. IR ν_{max}^{KBr} cm^{-1}: 1730 (CO_2CH_3), 1680 (C=O). *Anal.* Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.58. Found: C, 73.67; H, 5.77.

2-Benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthalenecarbaldehyde Ethylene Acetal (**11**)——A mixture of **8** (2.0 g), ethylene glycol (5 ml) and *p*-toluenesulfonic acid (20 mg) in benzene (50 ml) was refluxed with continuous removal of water for 2 hr. The cooled reaction mixture was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from ether–*n*-hexane to give **11** (2.0 g, 87%) as white crystals, mp 88—89°. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=O). NMR ($CDCl_3$) δ: 4.43 (1H, s, $-CH\langle^{O}_{O}$). *Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.12; H, 6.46.

2-Benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthalenecarbaldehyde Aldoxime (**12**)——A mixture of **8** (7.6 g), $NH_2OH \cdot HCl$ (1.98 g) and AcONa (2.5 g) in EtOH (100 ml) was stirred at room temperature for 3 hr then poured into water. The resulting precipitate was collected by filtration, washed with water and recrystallized from EtOH to give **12** (5.9 g, 74%) as pale yellow needles, mp 171—173°. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 1580 (C=N–). *Anal.* Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.48; H, 5.65; N, 4.53.

2-Benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthonitrile (**13**)——To a cooled solution of **12** (5.9 g) in pyridine (30 ml) was added benzenesulfonyl chloride (5.3 g). The mixture was stirred at room temperature for 15 hr then poured into ice-water. The resulting precipitate was collected by filtration, washed with water and recrystallized from EtOH to afford **13** (4.7 g, 85%) as pale yellow needles, mp 140—141°. IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1680 (C=O). *Anal.* Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.92; H, 5.40; N, 4.94.

Methyl 2-Hydroxy-5,6,7,8-tetrahydro-1-naphthoate (**15**)——A solution of **14** (417 g) in MeOH (3 l) was hydrogenated (100 kg/cm^2) at 60—80° with 5% Pd–C (150 g). After absorption of two equimolecular amounts of H_2, the cooled reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was distilled to afford **15** (271 g, 64%) as a colorless oil, bp 123—125°/0.6 mmHg. IR ν_{max}^{film} cm^{-1}: 1730, 1660 ($COOCH_3$). NMR ($CDCl_3$) δ: 1.5—2.0 (4H, m, $-CH_2-$), 2.5—2.8 (2H, broad, $-CH_2-$), 2.8—3.1 (2H, broad, $-CH_2-$), 3.94 (3H, s, CO_2CH_3), 6.73 (1H, d, $J=8$ Hz), 7.09 (1H, d, $J=8$ Hz), 10.79 (1H, s, OH). This compound was almost pure (>95%) and used for the next reaction.

Methyl 2-Benzyloxy-5,6,7,8-tetrahydro-1-naphthoate (**16**)——A mixture of **15** (117 g), benzyl chloride (72 g) and anhydrous K_2CO_3 (80 g) in DMF (500 ml) was heated at 100° for 5 hr under stirring, then poured into ice-water. The resulting precipitate was collected by filtration, washed with water and recrystallized from MeOH, yielding **16** (122 g, 82%) as colorless prisms, mp 59—61°. *Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.06; H, 6.75.

Formation of 10 *via* Oxidation of 16 with Chromic Acid——A solution of chromic anhydride (90 g) in AcOH (210 ml) and water (30 ml) was added dropwise to a solution of **16** (122 g) in AcOH (500 ml) with stirring and ice-cooling at 10—15°. After stirring for a further 3 hr, the excess oxidizing agent was decomposed with MeOH. Water was added to the reaction mixture which was then extracted with benzene. The organic layer was washed with water, 5% $NaHCO_3$, then water, and dried over Na_2SO_4 then evaporated to dryness *in vacuo*. The residual pale yellow oil crystallized on standing at room temperature (111 g, 83%). IR and NMR spectra were identical with those of **10** derived from **2**.

2-Benzyloxy-6-bromo-5-oxo-5,6,7,8-tetrahydro-1-naphthonitrile (17)——To a solution of **13** (4.7 g) in AcOH (70 ml) was added pyridine hydrobromide perbromide (5.41 g) in small portions at room temperature with stirring. The mixture was stirred for a further 2 hr. The reaction mixture was condensed *in vacuo*. The residue dissolved in AcOEt was washed with water, 5% $NaHCO_3$ then water, and dried over Na_2SO_4 then evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt–*n*-hexane to give **17** (4.9 g, 81%) as colorless needles, mp 113—115°. IR ν_{max}^{KBr} cm^{-1}: 2220 (C≡N), 1690 (C=O). NMR ($CDCl_3$) δ: 4.70 (1H, t, J=4 Hz, >C<u>H</u>–Br). *Anal.* Calcd. for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.39. Found: C, 60.45; H, 3.78; N, 3.10.

Methyl 2-Benzyloxy-6-bromo-5-oxo-5,6,7,8-tetrahydro-1-naphthoate (18)——Similarly, **18** was prepared from **10** in 85% yield. mp 130—131°. IR ν_{max}^{KBr} cm^{-1}: 1740 (CO_2CH_3), 1690 (C=O). NMR ($CDCl_3$) δ: 4.67 (1H, t, J=4 Hz, >C<u>H</u>–Br). *Anal.* Calcd. for $C_{19}H_{17}BrO_4$: C, 58.63; H, 4.42. Found: C, 58.43; H, 4.26.

2-Benzyloxy-6-N-methylbenzylamino-5-oxo-5,6,7,8-tetrahydro-1-naphthonitrile (19)——A mixture of **17** (2.0 g) and N-methylbenzylamine (2.0 g) in dry benzene was refluxed in a stream of N_2 for 5 hr. AcOEt and H_2O were added to the cooled reaction mixture which was then shaken. The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to give **19** (1.28 g, 58%) as pale brown plates, mp 142—143°. IR ν_{max}^{KBr} cm^{-1}: 2220 (CN), 1680 (C=O). NMR ($CDCl_3$) δ: 2.36 (3H, s, NCH_3), 3.69, 3.89 (2H, d, J=14 Hz, NCH_2Ph), 5.22 (2H, s, $PhCH_2O$–), 6.90 (1H, d, J=9 Hz, 3-H), 8.10 (1H, d, J=9 Hz, 4-H). *Anal.* Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.62; H, 5.94; N, 7.05.

***cis*- and *trans*-2-Benzyloxy-6-N-methylbenzylamino-5-hydroxy-5,6,7,8-tetrahydro-1-naphthonitrile (22 and 20) *via* Reduction of 19**——a) A mixture of **19** (1.28 g) and $NaBH_4$ (500 mg) in EtOH (40 ml) and THF (20 ml) was stirred at room temperature for 4 hr. The reaction mixture was condensed to *ca.* 10 ml *in vacuo*, then poured into water and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue with a 3: 1 ratio of **20** to **22** according to the NMR spectrum, was chromatographed on silica gel (100 g) using $CHCl_3$ as the eluant. The first effluent was evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt–*n*-hexane to give **20** (320 mg, 25%) as colorless prisms, mp 140—141°. NMR ($CDCl_3$) δ: 2.26 (2H, s, NCH_3), 4.55 (1H, d, J=10 Hz, >C<u>H</u>–OH), 6.82 (1H, d, J=9 Hz, 3-H), 7.67 (1H, d, J=9 Hz, 4-H). *Anal.* Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.23; H, 6.42; N, 6.97. The second fraction was worked up similarly to give **22** (150 mg, 12%) as colorless plates recrystallized from AcOEt–*n*-hexane, mp 141—142°. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 2230 (CN). NMR ($CDCl_3$) δ: 2.28 (3H, s, NCH_3), 4.71 (1H, d, J=3 Hz, >C<u>H</u>–OH), 5.16 (2H, s, $PhCH_2O$–), 6.83 (1H, d, J=9 Hz, 3-H), 7.50 (1H, d, J=9 Hz, 4-H). *Anal.* Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.38; N, 7.29.

b) To a solution of **19** (900 mg) in THF (30 ml) was added $LiAlH(O\text{-}t\text{-}Bu)_3$ (900 mg), the mixture was stirred at room temperature for 6 hr. After addition of MeOH, the reaction mixture was poured into ice-water and extracted with benzene. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The crude mixture obtained consisted of **20** and **22** in a ratio of 1: 2.

Methyl *cis*- and *trans*-2-Benzyloxy-5-hydroxy-6-N-methylbenzylamino-5,6,7,8-tetrahydro-1-naphthoate (23 and 21)——A mixture of **18** (500 mg) and N-methylbenzylamine (350 mg) in ethyl methyl ketone (6 ml) was heated at 60° in a nitrogen atmosphere for 3 hr. The cooled reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with water dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a pale yellow oil (450 mg). The crude oil was dissolved in EtOH (6 ml), and $NaBH_4$ (80 mg) was added to the solution. The mixture was stirred at room temperature for 2 hr, then poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene–acetone (10: 1) as the eluant to give **21** and **23**, which were isolated as hydrochloride. **21** (150 mg), white crystals (MeOH-iso-Pr_2O), mp 225—226° (dec.). *Anal.* Calcd. for $C_{27}H_{30}ClNO_4$: C, 69.29; H, 6.46; N, 2.99. Found: C, 69.23; H, 6.25; N, 2.84. **23** (100 mg), white crystals (MeOH-iso-Pr_2O), mp 245—246° (dec.). *Anal.* Calcd. for $C_{27}H_{30}ClNO_4$: C, 69.29; H, 6.46; N, 2.99. Found: C, 69.35; H, 6.33; N, 3.06.

Reaction of 18 with N-*tert*-Butylbenzylamine——A mixture of **18** (500 mg) and N-*tert*-butylbenzylamine (1.0 g) in acetonitrile (10 ml) was refluxed in a nitrogen atmosphere for 5 hr, then evaporated to dryness *in vacuo*. The residue was purified by preparative TLC using $CHCl_3$–EtOH (10: 3) as the developing solvent to give methyl 2-benzyloxy-5-hydroxy-1-naphthoate (**24**) as a pale yellow oil. IR ν_{max}^{film} cm^{-1}: 3400—3350 (OH), 1700 (CO_2CH_3). NMR ($CDCl_3$) δ: 3.39 (3H, s, CO_2CH_3), 5.05 (2H, s, $PhCH_2O$–), 6.51 (1H, d, d, J=6, 2 Hz), 7.00 (1H, d, J=9 Hz), 7.0—7.5 (7H, m), 8.13 (1H, d, J=9 Hz). MS *m/e*: 308 (M^+).

Oximation of 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenones——Oximation of 5-substituted 6-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenones was carried out by using of hydroxylamine hydrochloride and AcONa in MeOH at room temperature. Table I shows the oximes (**25**—**28**) obtained.

Formation of 5-Substituted 6-Benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone Oxime-O-benzenesulfonates (29—32)——To a solution of 5-substituted 6-benzyloxy-3,4-dihydro-1(2*H*)-naphthalenone oxime (10 mmol) in dry pyridine (20 ml) was added dropwise benzenesulfonyl chloride (12 mmol) under stirring and ice-cooling. The mixture was stirred for 3—5 hr and left to stand in a refrigerator overnight, poured into ice-water. The resulting precipitate was collected by filtration, washed with water and recrystallized to give the oxime-O-

benzenesulfonate (Table II).

Methyl 6-Amino-2-benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthoate Hydrochloride (33)——To an ethanolic solution of potassium ethoxide prepared from metallic K (3.0 g) and abs. EtOH (80 ml), a solution of **29** (23 g) in dry benzene (100 ml) was added dropwise at 0—5° with stirring in a nitrogen atmosphere. The mixture was stirred for a further 8 hr at 10° and filtered. The filtrate was added dropwise to conc. HCl (50 ml) with stirring and ice-cooling. The resulting precipitate was collected by filtration and recrystallized from MeOH (charcoal) to give **33** (11.3 g, 63%) as pale yellow prisms, mp 205—210° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1730, 1680, 1580. NMR (DMSO-d_6) δ: 3.85 (3H, s, CO_2CH_3), 4.36 (1H, d, d, J=14, 5 Hz, >C<u>H</u>–NH_2), 5.30 (2H, s, $PhCH_2O$–), 8.02 (1H, d, J=8 Hz, 4-H). *Anal.* Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 62.77; H, 5.63; N, 3.79.

6-Amino-2-benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthalenecarbaldehyde Hydrochloride (34)——Similarly, **34** was prepared from **30** in 35% yield. Pale yellow needles (MeOH), mp 180—185° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR (DMSO-d_6) δ: 5.38 (2H, s, OCH_2Ph), 8.15 (1H, d, J=9 Hz, 4-H), 10.56 (1H, s, CHO). MS *m/e*: 295 (M^+).

6-Amino-2-benzyloxy-5-oxo-5,6,7,8-tetrahydro-1-naphthonitrile Hydrochloride (35)——Similarly, **35** was prepared from **31** in 85% yield. Colorless prisms (MeOH), mp 208—213° (dec.). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1700 (C=O). NMR (DMSO-d_6) δ: 5.40 (2H, s, OCH_2Ph), 4.39 (1H, d, d, J=12, 4 Hz, >C<u>H</u>–NH_2), 8.16 (1H, d, J=9 Hz, 4-H). MS *m/e*: 292 (M^+).

2-Amino-6-benzyloxy-5-methoxymethyl-3,4-dihydro-1(2*H*)-naphthalenone Hydrochloride (36)——Similarly, **36** was prepared from **32** in 15% yield. White crystals (EtOH–AcOEt), mp 180—190° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR (DMSO-d_6) δ: 3.26 (3H, s, $-CH_2OC\underline{H}_3$), 4.54 (2H, s, $-CH_2O$–), 7.20 (1H, d, J=9 Hz, 7-H), 7.95 (1H, d, J=9 Hz, 8-H). MS *m/e*: 311 (M^+).

Methyl 2-Benzyloxy-6-isopropylamino-5-oxo-5,6,7,8-tetrahydro-1-naphthoate Hydrochloride (37)——To a solution of **33** (1.0 g) in acetone (5 ml) and MeOH (10 ml), lithium cyanoborohydride (500 mg) was added in small portions with stirring and ice-cooling in a nitrogen atmosphere. After stirring for a further 4 hr, ethanolic HCl was added and the mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH (charcoal) to give **37** (1.0 g, 89%) as colorless needles, mp 188—191° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1725 (CO_2CH_3), 1690 (C=O), 1580. NMR (DMSO-d_6) δ: 1.27, 1.32 (6H, d, J=6 Hz, iso-Pr), 4.47 (1H, d,d, J=14,4 Hz, >C<u>H</u>–NH–), 7.98 (1H, d, J=8 Hz, 4-H). *Anal.* Calcd. for $C_{22}H_{26}ClNO_4$: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.38; H, 6.25; N, 3.45.

Methyl 2-Benzyloxy-6-cyclobutylamino-5-oxo-5,6,7,8-tetrahydro-1-1naphthoate Hydrochloride (38)——Similarly, **38** was prepared from **33** and cyclobutanone in 61% yield. White crystals, mp 165—175° (dec). *Anal.* Calcd. for $C_{23}H_{26}ClNO_4$: C, 66.42; H, 6.30; N, 3.37. Found: C, 65.61; H, 6.35; N, 3.41.

2-Benzyloxy-6-isopropylamino-5-oxo-5,6,7,8-tetrahydro-1-naphthonitrile Hydrochloride (39)——Similarly, **39** was prepared from **35** and acetone in 74% yield. Colorless prisms, mp 195—199° (dec.). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1675 (C=O). NMR (DMSO-d_6) δ: 1.30, 1.35 (6H, d, J=6 Hz, iso-Pr), 8.15 (1H, d, J=9 Hz, 4-H). MS *m/e*: 334 (M^+).

Methyl *trans*-6-Amino-2-benzyloxy-5-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (40)——To a suspension of $NaBH_4$ (3.0 g) in EtOH (100 ml) was added **33** (12.7 g) in small portions with stirring at room temperature. After stirring for 2 hr, the reaction mixture was poured into water. The resulting precipitate was collected by filtration and recrystallized from AcOEt to give **40** (10.1 g) as colorless prisms, mp 124—126°. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO_2CH_3), 1590, 1580. NMR (DMSO-d_6) δ: 3.76 (3H, s, CO_2CH_3), 4.08 (1H, d, J= 8 Hz, 5-H), 5.10 (2H, s, $PhCH_2O$–), 6.97 (1H, d, J=8 Hz, 3-H), 7.49 (1H, d, J=8 Hz, 4-H). Similar reduction of 2-amino- (**35**) and 2-alkylamino-3,4-dihydro-1(2*H*)-naphthalenone (**37, 38, 39**) by $NaBH_4$ afforded the corresponding *trans*-amino alcohols (**42, 43, 45, 47**).

Reduction of 33 with Diborane and Formation of Methyl *cis*-6-Amino-2-benzyloxy-5-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (41)——To an ice-cooled suspension of **33** (6 g) in THF (200 ml) freshly distilled from $LiAlH_4$, was introduced diborane produced from BF_3 etherate (30 ml) in diglime (40 ml) and $NaBH_4$ (9 g) in diglime (200 ml). The mixture was stirred for 20 hr at room temperature, and became a transparent solution. It was filtered and ethanolic HCl was added to the filtrate. The resulting precipitate was collected by filtration and washed with THF to give a mixture of **40** and **41** (1: 2) isolated as the hydrochloride (4.2 g). Recrystallization of the mixture from MeOH gave pure **41** (1.75 g, 38%) as colorless plates, mp 220—222° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1730 (CO_2CH_3), 1590. Similar reduction of **38** with diborane gave a mixture of **45** and **46** (5—4: 1).

Reductive N-Alkylation of Methyl *cis*- and *trans*-6-Amino-2-benzyloxy-5-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (41 and 40)——a) A mixture of **41** (5.0 g) and cyclobutanone (2.0 g) in benzene (30 ml) was heated at 60—70° for 3 hr and refluxed for 3 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in EtOH (30 ml) and $NaBH_4$ (600 mg) was added. The mixture was stirred for 30 min at room temperature and poured into water and extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt–*n*-hexane to give **46** (4.6 g, 78%). Compounds **43—45** were prepared by similar method.

b) To a solution of **40** (2 mmol) and carbonyl compounds (2.5 mmol) in MeOH (20 ml) was added lithium

cyanoborohydride (2.3 mmol) at room temperature with stirring. After stirring for 4—5 hr, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized to give the N-alkylated compounds (**48**—**51**), Table III.

Methyl *trans*-2-Benzyloxy-6-ethoxycarbonylamino-5-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (52)——To a mixture of **40** (1.0 g) and ethyl chloroformate (400 mg) in AcOEt (20 ml) and water (5 ml) was added anhydrous K_2CO_3 (1.0 g) in small portions with vigorous stirring. After stirring for 1 hr, the organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to afford **52** (922 mg, 78%) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1730 (CO_2-CH_3), 1690 (NHCOO–). NMR ($CDCl_3$) δ: 4.43 (1H, d, J=7 Hz, >C<u>H</u>–OH).

Methyl *trans*-5-Acetoxy-6-acetylamino-2-benzyloxy-5,6,7,8-tetrahydro-1-naphthoate (53)——A mixture of **40** (1.0 g) and Ac_2O (3 ml) in pyridine (15 ml) was stirred at room temperature for 30 hr, then poured into ice–water. The resulting precipitate was collected by filtration, washed with water and recrystallized from AcOEt-isopropyl ether to give **53** (1.04 g, 83%) as colorless needles, mp 171—172°. IR ν_{max}^{KBr} cm^{-1}: 1730, 1645. NMR ($CDCl_3$) δ: 1.89 (3H, s), 2.04 (3H, s), 5.79 (1H, d, J=7 Hz, >C<u>H</u>–OAc). *Anal.* Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.08; H, 6.10; N, 3.37.

***trans*-6-Benzyloxy-5-hydroxymethyl-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol (57)**——To a suspension of $LiAlH_4$ (2.5 g) in THF (20 ml) freshly distilled from $LiAlH_4$ was added dropwise a solution of **43** (6.0 g) in THF (20 ml) with stirring in a nitrogen atmosphere. The mixture was refluxed for 3 hr. After decomposition of the excess $LiAlH_4$ with MeOH and 20% NaOH, the reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to give **57** (4.68 g, 86%) as colorless prisms. 5-Hydroxymethyl derivatives (**54**—**64**) were prepared by similar $LiAlH_4$ reductions of the corresponding 5-methoxycarbonyl derivatives (Table III).

***trans*-6-Benzyloxy-2-isopropylamino-5-ureidomethyl-1,2,3,4-tetrahydro-1-naphthalenol (65)**——To a suspension of $LiAlH_4$ (120 mg) in THF (10 ml) freshly distilled from $LiAlH_4$ was added dropwise a solution of **47** (500 mg) in THF (20 ml). The mixture was refluxed for 2 hr. After decomposition of the excess $LiAlH_4$ with MeOH and 20% NaOH, the reaction mixture was poured into ice-water, then extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in AcOEt and treated with ethanolic HCl to afford the crude hydrochloride of the 5-aminomethyl derivative (560 mg). To a solution of this salt (560 mg) in EtOH (20 ml) and water (6 ml) was added KCNO (200 mg). The mixture was refluxed for 3 hr then poured into ice-water containing $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt–EtOH to give **65** (285 mg, 51%) as white crystals.

Formation of 1a—p *via* Removal of Benzyl Group by Catalytic hydrogenation——A solution of 5-substituted 2-amino- and 2-alkylamino-6-benzyloxy-1,2,3,4-tetrahydro-1-naphthalenols (2 mmol) in MeOH (15 ml) was hydrogenated using 5% palladium charcoal (50 mg) at room temperature under an atmospheric pressure. After absorption of one equivalent molecule of H_2, the reaction mixture was filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized to give **1a**—**1p** (Table IV).

Formation of Oxazolidin-2-one Derivatives (66 and 67) from 40 and 41 by Reaction with Phosgen——To an ice-cooled solution of **40** or **41** (3 mmol) in THF (20 ml) containing triethylamine (7 mmol) was added dropwise a 10% solution of phosgen in toluene (3.5 mmol) with stirring. The mixture was stirred for further 2 hr, then poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized to give **66** or **67**, respectively. **66**: Colorless prisms, mp 204—206°. Yield 78%. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1730, 1600, 1580. NMR ($CDCl_3$) δ: 3.6—3.8 (1H, m, >C<u>H</u>–N–), 3.89 (3H, s, CO_2CH_3), 4.98 (1H, d, J=11.5 Hz, >C<u>H</u>–O–), 5.10 (2H, s, $PhCH_2O$–), 5.63 (1H, s, NH). *Anal.* Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.09; H, 5.35; N, 3.93. **67**: White crystals (aqueous MeOH), mp 135—137°. Yield 85%. IR ν_{max}^{Nujol} cm^{-1}: 3240 (NH), 1740 (shoulder), 1725, 1700, 1600, 1590 (shoulder). NMR ($CDCl_3$) δ: 3.89 (3H, s, CO_2CH_3), 4.1—4.3 (1H, m, >C<u>H</u>–N–), 5.12 (2H, s, $PhCH_2O$–), 5.52 (1H, d, J=8 Hz, >C<u>H</u>–O–), 6.30 (1H, s, NH). *Anal.* Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.68; H, 5.39; N, 3.99.

Acknowledgement The authors are grateful for Drs. E. Ohmura, H. Morimoto and K. Morita for encouragement and helpful advices throughout the work.