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Synthesis of 2-N,N-Dialkylamino-1-aroyloxybenzocycloalkanes[1]

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Aroyl esters of 2-N,N-dialkylamino-1-benzocycloalkanols (**6**, **7**), which may be considered to be semi-rigid cyclic analogs of procaine, were prepared to study the influence of the stereochemical relationship between the aroyloxy and the amino group on local anesthetic activity. The *cis*-compounds (**6a-1**, **6c-1**) were more active than the corresponding *trans*-isomers (**6b-1**, **6d-1**). Similarly, the optical isomers of *cis*-2-N,N-dimethylamino-1-benzoyloxy-1,2,3,4-tetrahydronaphthalene (**6c-1**) differed in their activity with the *l*-isomer being more active. The reaction of 2-bromo-1-tetralol (**9**) with dimethylamine was also discussed.

Keywords——local anesthetic; structure-activity relationship; indanol dialkylamino; tetralol dialkylamino; benzocycloheptanol dialkylamino; ester benzoate; optical resolution; bromotetralol reaction dimethylamine

The influence of the stereochemical structure of the local anesthetic molecule on the activity has been recognized in some cases,[3] *e.g.* the *cis* and *trans* isomers of 2-N,N-dialkylamino-1-cyclohexyl carbanilate[3b] and the enantiomers of N-*n*-butyl-3-piperidyl 2-chloro-6-methylcarbanilate.[3c] In the case of optically active prilocaines, α-propylamino-2-methylpropionanilide, the difference in their local anesthetic activities was found *in vivo* but not *in vitro*.[3d] In general, however, the evalution of stereochemical factros in the local anesthetic activity seems to be difficult because most of the anesthetics have flexible molecular structures except for rather complex ones like cocaine and belong to many different chemical classes.

In order to obtain further information about the stereochemical relationship between the benzoyloxy and the amino group on local anesthetic activity, we chose *cis*- and *trans*-2-N,N-dialkylamino-1-aroyloxybenzocycloalkanes as model compounds since they may be simple semi-rigid cyclic analogs of procaine or USVP-64105, the hydrochloride of 2-N,N-diethylamino-1-phenylethyl benzoate. The latter is considered in its chemical structure to be derived from benzoyl ester of β-N,N-diethylaminoethanol by introducing a phenyl group at its α-carbon and reported to be more active in the local anesthesia than the original compound.[4]

This paper describes the synthesis of aroyl esters of *dl-cis*- and *trans*-2-N,N-dialkylamino-1-indanols, *dl -cis*- and *trans*-2-N,N-dialkylamino-1-tetralols and *dl-cis*-6-N,N-dimethylamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol as well as the resolution of *dl cis*-1-benzoyloxy-2-N,N-dimethylamino-1,2,3,4,tetrahydronaphthalene. The preliminary evaluation of their anesthetic activities is also included.[5]

1) The 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, Apr. 1975.
2) Location: *1–1–8, Azusawa, Itabashi-ku, Tokyo.*
3) *a*) J. Büchi and X. Perlia, "Drug Design," Vol. 3, ed. by E.J. Ariëns, Academic Press, New York and London, 1972, Chapter 6; *b*) L. Beněs, A. Borovanský, and L. Kopáčová, *Arch. Pharm.*, **305**, 648 (1972); *c*) B. Åkerma, *Acta Pharmacol. Toxicol.*, **32**, 97 (1963); *d*) B. Åkerman, H. Persson, and C. Tegner, *Acta Pharmacol. Toxicol.*, **25**, 233 (1967).
4) S.L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959); J.M. Classman, F. Rauzzino, D.V. Romano, and G. Ramachander, *Pharmacologist*, **12**, 308 (1970).
5) The details of pharmacological activity of these compounds was reported by M. Takeda, *J. Pharm. Soc. Japan*, **96**, 26 (1976).

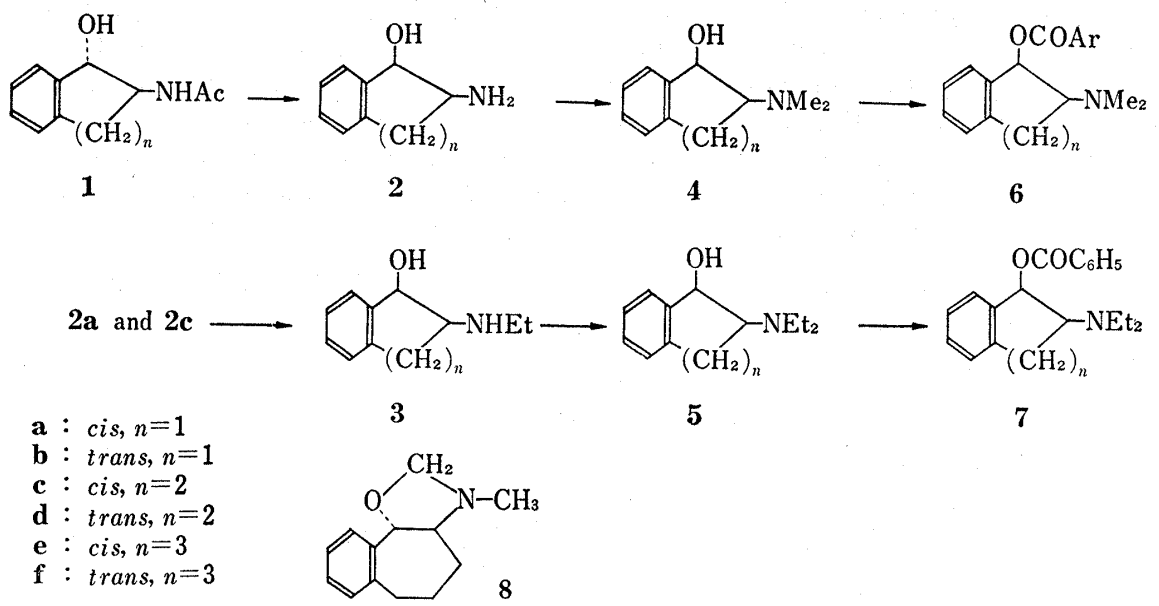


Chart 1

The synthetic route starting with *trans*-2-acetamido-1-benzocycloalkanol (**1**) is presented in Chart 1. Aminoalcohol (**2**) was prepared by the known methods.[6] Methylation of **2** with formic acid and formalin followed by acylation gave dimethylamino ester (**6**). Diethyl derivatives (**7**) could be prepared by benzoylation of diethylaminoalcohol (**5**), which was obtained by treating ethylaminoalcohol (**3**)[7] with ethyl iodide in acetone in the presence of anhydrous potassium carbonate. The resolution of *dl-cis*-1-benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene (**6c-1**) with dibenzoyl-*d*-tartaric acid gave *d*-**6c-1** hydrochloride, mp 210—212°, $[\alpha]_D^{20}$+177.2° (c=1.73, ethanol) and *l*-**6c-1** hydrochloride, mp 211—212°, $[\alpha]_D^{20}$−175.3° (c=1.09, ethanol).

Seven-membered *cis*-dimethylamino ester (**4e**) was readily prepared from the corresponding *cis*-aminoalcohol (**2e**) by methylation with formalin and formic acid and following benzoylation. Whereas the *trans* isomer (**2f**) upon exposure to the above methylation condition gave an unexpected product (**8**) in quantitative yield. The structure of **8** was determined on the basis of its spectral properties. The nuclear magnetic resonance(NMR) spectrum of **8** exhibited a three proton singlet at δ 2.27 (N–CH_3) and two proton AB type doublets at δ 4.07 and 4.77 (OCH_2N, J=2 Hz), and the mass spectrum showed the molecular ion peak (m/e=203). The esters obtained in the present work are summarized in Table I.

Among these compounds, the synthesis of 2-N,N-dimethylamino-1-tetralol from bromohydrin (**9**) and dimethylamine[8] and its esters such as benzoyl,[8a] *p*-nitrobenzoyl[8b] and *p*-aminobenzoyl[8c] had been reported. But, von Braun and Weissbach[9] later corrected that the product, obtained by the reaction of **9** with dimethylamine, should be 1-N,N-dimethylamino-2-tetralol (**10**) on the basis of chemical evidences.

6) *a*) F. Zymalkowski and H.J. Rimek, *Arch. Pharm.*, **294**, 581 (1961); *b*) R.I. Trift, *J. Chem. Soc.* (*C*), **1967**, 288; *c*) H.J. Rimek, T. Yupraphat, and F. Zymalkowski, *Ann.*, **725**, 116 (1969); *d*) C.F. Huebner, E.M. Donoghue, C.T. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.*, **35**, 1149 (1970); *e*) T. Yupraphat, H.J. Rimek, and F. Zymalkowski, *Ann.*, **738**, 79 (1970); *f*) J.M. Khanna, J. Bolger, and N. Anand, *Indian J. Chem.*, **7**, 550 (1969).

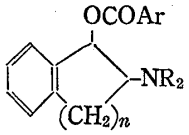
7) *a*) H.J. Rimek, T. Yuprophat, and F. Zymalkowski, *Ann.*, **726**, 25 (1969); *b*) F. Zymalkowski, T. Yupraphat, and K. Schmeisser, *Arch. Pharm.*, **301**, 321 (1968).

8) *a*) J. von Braun, O. Braunsdorf, and G. Kirschbaum, *Chem. Ber.*, **55**, 3648 (1922); *b*) A. Gonzalez and M. Campoy, *Anales soc. espan. fis quím.*, **20**, 534 (1922); *c*) F. Straus and A. Rohrbacher, *Chem. Ber.*, **54**, 40 (1921).

9) J. von Braun and K. Weissbach, *Chem. Ber.*, **63**, 3052 (1930).

Structural assignment of **10** was further strengthened by the NMR measurements. As Table II shows, the higher field shift (*ca.* 1 ppm) of C–1 and the lower field shift (*ca.* 1 ppm) of C–2 hydrogens of **10** than those of **4c** and **4d** and the relatively larger coupling constant (9 Hz) between C–1 and C–2 hydrogens, corresponding to *trans* configuration were obserbed. Accordingly, the reported esters should be *trans*-2-benzoyloxy-(**11a**), *trans*-2-*p*-nitrobenzoyloxy- (**11b**) and *trans*-2-*p*-aminobenzoyloxy-1-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene (**11c**) which are different from the compounds now investigated.

TABLE I. 2-N,N-Dialkylamino-1-aroyloxybenzocycloalkane (**6**, **7**)



Compd. No.	Configuration	*n*	R	Ar	Procedure	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
6a-1	*cis*	1	CH_3	C_6H_5	A	220 ($EtOH–C_6H_6$)	$C_{18}H_{19}O_2N\cdot HCl$	68.03 (68.21)	6.34 (6.54)	4.41 (4.36)
7a-1	*cis*	1	C_2H_5	C_6H_5	A	197—198 (EtOH–AcOEt)	$C_{20}H_{23}O_2N\cdot HCl$	69.45 (69.36)	6.99 (6.78)	4.05 (4.21)
6b-1	*trans*	1	CH_3	C_6H_5	D	125—127 ($EtOH–C_6H_6$)	$C_{18}H_{19}O_2N\cdot HCl$	68.03 (67.82)	6.34 (6.19)	4.41 (4.57)
6c-1	*cis*	2	CH_3	C_6H_5	A or B	74—75 (C_6H_5–*n*-hexane)	$C_{19}H_{21}O_2N$	77.26 (77.17)	7.17 (6.91)	4.74 (4.94)
6c-1 Hydrochloride						203—204 (EtOH–AcOEt)	$C_{19}H_{21}O_2N\cdot HCl$	68.77 (68.51)	6.68 (6.75)	4.22 (4.39)
d-**6c-1** Hydrochloride						210—211 (EtOH)	$[\alpha]_D^{20}+177.2$($c=1.73$, EtOH)			
l-**6c-1** Hydrochloride						211—212 (EtOH–ether)	$[\alpha]_D^{20}-175.3$($c=1.09$, EtOH)			
6c-2	*cis*	2	CH_3	4-$CH_3C_6H_4$	C	187—189 (EtOH–ether)	$C_{20}H_{23}O_2N\cdot HCl$	69.45 (69.59)	6.99 (6.78)	4.05 (4.21)
6c-3	*cis*	2	CH_3	$C_6H_5CH=CH$	B	100—105 (EtOH–H_2O–ether)	$C_{21}H_{23}O_2N\cdot HCl\cdot H_2O$	67.10 (66.50)	6.97 (6.57)	3.73 (4.17)
6c-4	*cis*	2	CH_3	4-$C_6H_5C_6H_4$	B	210—212 (iso-PrOH)	$C_{25}H_{25}O_2N\cdot HCl$	73.61 (73.74)	6.42 (6.58)	3.43 (3.31)
6c-5	*cis*	2	CH_3	4-$NO_2C_6H_4$	B	173—175 (EtOH)	$C_{19}H_{20}O_4N_2\cdot HCl$	60.56 (60.67)	5.62 (5.46)	7.43 (7.58)
6c-6	*cis*	2	CH_3	4-$NH_2C_6H_4$	E	160—161 (C_6H_6)	$C_{19}H_{22}O_2N_2$	73.52 (73.66)	7.14 (7.03)	9.02 (9.18)
6c-7	*cis*	2	CH_3	3,4,5-triMeOC_6H_2	B	147—149 (EtOH)	$C_{22}H_{27}O_5N\cdot HCl$	62.63 (62.52)	6.67 (6.75)	3.32 (3.19)
6c-8	*cis*	2	CH_3	2-MeO-4-$NO_2C_6H_3$	B	207—208 (EtOH)	$C_{20}H_{22}O_5N_2\cdot HCl$	59.04 (59.27)	5.70 (5.51)	6.89 (6.98)
6c-9	*cis*	2	CH_3	2-MeO-4-$NH_2C_6H_3$	E	202—203 (EtOH)	$C_{20}H_{24}O_3N_2$	70.57 (70.39)	7.11 (7.25)	8.23 (8.04)
6c-10	*cis*	2	CH_3	4-$Me_2NC_6H_4$	B	215—216 (EtOH–AcOEt)	$C_{21}H_{26}O_2N_21/2$ $H_2O\cdot HCl$	65.70 (65.69)	7.35 (7.11)	7.30 (7.34)
6c-11	*cis*	2	CH_3	3,4-diClC_6H_3	C	182—183 (EtOH)	$C_{19}H_{19}O_2NCl_2\cdot HCl$	56.95 (56.73)	5.03 (5.21)	3.50 (3.43)
6d-1	*trans*	2	CH_3	C_6H_5	A	79 (H_2O)	$C_{19}H_{21}O_2N\cdot H_2O\cdot HCl$	65.23 (65.66)	6.91 (6.42)	4.00 (4.13)
7c-1	*cis*	2	C_2H_5	C_6H_5	B	oil	$C_{21}H_{25}O_2N\cdot HCl$	70.08 (70.62)	7.28 (7.02)	3.89 (3.58)
6e-1	*cis*	3	CH_3	C_6H_5	B	218—220 ($EtOH–C_6H_6$)	$C_{20}H_{23}O_2N\cdot HCl$	69.45 (69.35)	6.99 (7.10)	4.05 (4.19)

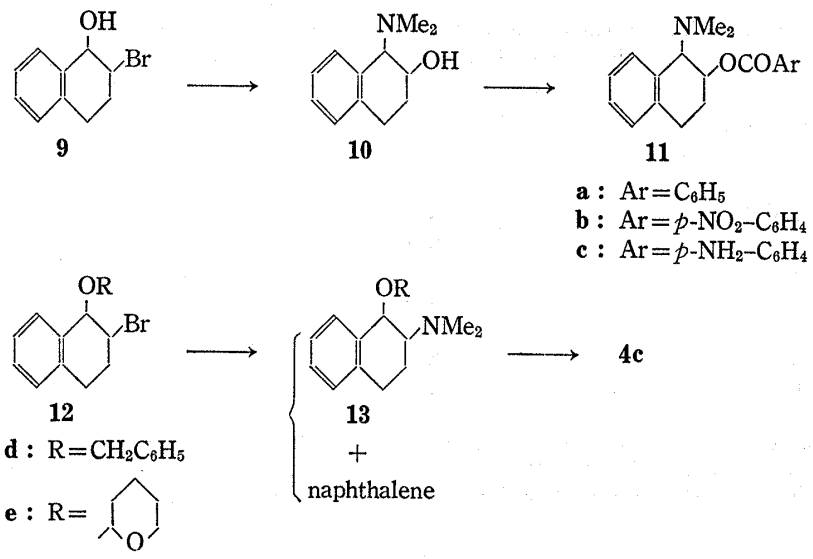


Chart 2

Table II. NMR Spectra of N,N-Dimethyl-tetralols (in $CDCl_3$)

Compd. No.	Chemical shift (δ) C-1H	Chemical shift (δ) C-2H	Coupling constant(Hz)
4c	4.74, d	2.20—2.60, m	4
4d	4.60, d	2.40—2.80, m	10
10	3.62, d	3.70—3.95, m	9

In contrast to **9**, bromohydrin derivative (**12**) whose hydroxy function was masked, gave *cis*-2-N,N-dimethylamino compound (**13**) when treated with dimethylamine. A treatment of benzyloxy compound (**12d**) with dimethylamine in benzene at 90—100° for 40 hours in a sealed tube gave dimethylamino compound (**13d**) along with a considerable amount of naphthalene. Similarly, heating of dihydropyranyl derivative (**12e**) with aquous dimethylamine in methanol at 90—100° for 20 hours in a sealed tube gave dimethylamino compound (**13e**) accompanied also with a comparable amount of naphthalene. Removal of the protecting groups from both **13d** and **13e** by the usual method gave *cis*-2-N,N-dimethylamino-1-tetralol (**4c**).

Thus, when the hydroxyl function of **9** was masked to prevent an epoxy intermediate formation, bromine atom at the 2 position was directly substituted by dimethylamino group to give the inverted or *cis*-2-N,N-dimethylamino compound (**13**).[10] The yield of **13** attempted under various conditions was low due to the competing elimination reaction forming naphthalene (Chart 2).

As Table III shows, the benzoyl esters of 2-N,N-dialkylamino-1-benzocycloalkanol had a potent local anesthetic activity in the guinea-pig corneal test. It was of interest that differential local anesthetic activity was found between the stereoisomers. The *cis* compounds (**6a-1**, **6c-1**) were more active than the corresponding *trans* isomers (**6b-1**, **6d-1**). In contrast to **6d-1**, its position isomer (**11a**) did not have any anesthetic activity. In addition, *l*-isomer of *cis*-1-benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene (**6c-1**) was more potent than the *d*-form in the activity.

10) The treatment of 1-benzyloxy-2-bromoindane with methylamine and the following hydrogenolysis was reported to give 1-hydroxy-2-methylaminoindane: R.V. Heinzelmann, B.O. Aspergren, and J.H. Hunter, *J. Org. Chem.*, **14**, 906 (1949). Recently its *cis* configuration was confirmed.[6d]

Table III. Surface Anesthetic Activities of Test Compounds and Reference Drugs in Guinea-pig Cornea

Compd. No.	EC_{50}[a] (% concentration)	Potency ratio
Procaine	2.0	1
USVP-64105	0.3	7
6a-1	0.08	25
6b-1	0.2	10
6c-1	0.07	29
6d-1	0.2	10
d-**6c-1**	0.2	10
l-**6c-1**	0.05	40

a) The EC_{50} values were determined for the first 30 minutes using groups of 8 animals according to the method of Chance and Lobstein.[b]
b) M.R.A. Chance and H. Lobstein, *J. Pharmacol. Exp. Ther.*, 82, 203 (1944).

Experimental[11]

General Preparation of 2-N,N-Dimethylamino-1-benzocycloalkanol (4)——A mixture of 2-amino-1-benzocycloalkanol (**2**) (0.01 mole), 85% formic acid (3 ml) and 35% formalin (2 ml) was heated at 100—110° for 4—7 hr. The reaction mixture was evaporated to dryness, the residue was treated with 30% K_2CO_3, and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and the solvent was removed *in vacuo* to give 2-N,N-dimethylamino-1-benzocycloalkanol (**4**) in the yield of 70—90%. The epimerization did not observed in this method.

cis-2-N,N-Dimethylamino-1-indanol (**4a**): mp 118—120° (from MeOH) (lit.[6d] mp 124—126°).

trans-2-N,N-Dimethylamino-1-indanol (**4b**): mp 111° (from AcOEt–ether) (lit.[6d] mp 105—107°).

cis-2-N,N-Dimethylamino-1-tetralol (**4c**): oil, NMR δ: 4.74 (1H, d, J=4 Hz, C-1H), 2.20—2.60 (1H, m, C-2H), 2.38 (6H, s, N–$CH_3\times2$). Mass Spectrum *m/e*: 191 (M^+). HCl salt: mp 183—185° (from EtOH–ether). *Anal.* Calcd. for $C_{12}H_{18}ONCl$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.41; H, 8.00; N, 5.91.

trans-2-N,N-Dimethylamino-1-tetralol (**4d**): oil. Mass Spectrum *m/e*: 191 (M^+). NMR δ: 4.60 (1H, d, J=10 Hz, C-1H), 2.40—2.80 (1H, m, C-2H), 2.36 (6H, s, N–$CH_3\times2$).

cis-6-N,N-Dimethylamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (**4e**): mp 132—134° (from benzene). *Anal.* Calcd. for $C_{13}H_{19}ON$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.06; H, 9.25; N, 6.74. NMR δ: 2.26 (6H, s, N–$CH_3\times2$), 4.95 (1H, d, J=4 Hz, C-5H). Mass Spectrum *m/e*: 205 (M^+).

Oxazolidine Derivative (8)——By the same treatment of **2f** as above, oily **8** was obtained in quantitative yield. Mass Spectrum *m/e*: 203 (M^+). NMR δ: 2.27 (3H, s, N–CH_3), 4.07 (1H, d, J=2 Hz, O–CH_2–N), 4.77 (1H, d, J=2 Hz, O–CH_2–N), 4.93 (1H, d, J=9 Hz, Ar–$\underset{\underset{O}{|}}{C}$–H), 1.00—2.90 (7H, methylene and methine proton) 7.00—7.80 (4H, aryl H).

***cis*-2-N,N-Diethylamino-1-indanol (5a)**——A mixture of *cis*-2-ethylamino-1-indanol (**3a**)[7a] (8 g), ethyl iodide (8.5 g), K_2CO_3 (12 g) and methyl ethyl ketone (70 ml) was refluxed for 20 hr. The reaction mixture was evaporated to dryness, the residue was treated with water, and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and evaporated to dryness. The residue was purified by chromatography over SiO_2 with $CHCl_3$–AcOEt to give 1.85 g of *cis*-2-N,N-diethylamino-1-indanol (**5a**), mp 56° (from *n*-hexane). NMR δ: 1.07 (6H, t, $CH_3\times2$), 2.5—3.8 (8H, m, OH, N–$CH_2\times2$, C-2 and C-3 H), 4.84 (1H, d, J=5 Hz, C-1H), 7.1—7.6 (4H, m, aryl H).

***cis*-2-N,N-Diethylamino-1-tetralol (5c)**——By a procedure similar to that for **5a**, from **3c**[7b] (5.7 g) was obtained oily **5c** (2.0 g). NMR δ: 1.04 (6H, t, $CH_3\times2$), 1.6—2.2 (2H, m, C-3H), 2.5—3.1 (6H, m, N–$CH_2\times2$ and C–4H), 3.9 (1H, b, OH), 4.65 (1H, d, J=4Hz, C-1H), 7.0—7.6 (4H, m, aryl H).

General Procedure for the Preparation of 1-Aroyloxy-2-N,N-dimethyl(and diethyl)amino-1,2,3,4-tetrahydronaphthalene (6 and 7)——A mixture of **4** or **5** (0.01 mole) and a corresponding acid chloride (0.011 mole) was treated in a solvent (5 ml) using the following procedures (A–D). After the reaction was over, the reaction mixture was evaporated to dryness, and the residue was recrystallized to give the hydrochloride of **6** and **7** in the yield of 70—90%. In the case of **6d-1** and **7c-1**, the free bases were purified by chromatography over SiO_2 and then treated with EtOH–HCl.

11) All melting points are not corrected. The spectra were recorded on the following instruments: IR, Hitachi EPI-G3; mass, Hitachi RMU-6MG; GC–MS, Hitachi RMU-6MG gas chromatography-mass spectrometer combined system; GC, Hewlett Packard 5710A; optical rotation, Perkin-Elmer 141 polarimeter; NMR, JEOL JNM-MH-100 using tetramenthylsilane as an internal standard and $CDCl_3$ as a solvent. Abbreviations: s=singlet, d=doublet, m=multiplet and br=broad.

A: The reaction mixture was refluxed in benzene for 3—8 hr with stirring.
B: In place of benzene as a solvent in A, CH_2Cl_2 was used.
C: In stead of refluxing in B, the reaction mixture was stirred for 15 hr at room temperature.
D: The reaction mixture was stirred in pyridine for 15 hr at 5—10° and evaporated to dryness. The residue was mixed with ice-water and extracted with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$, evaporated, and the residue was treated with EtOH–HCl.

E: Amino compounds (**6c-6** and **6c-9**) were obtained from nitro derivatives (**6c-5** and **6c-8**) by a usual procedure, illustrated by the preparation of **6c-6** as followes.

A mixture of **6c-5** (1 g), iron powder (1 g), EtOH (10 ml), H_2O (3 ml) and two drops of concd. HCl was heated at 80° for 25 min with stirring. Powdered $NaHCO_3$ (0.5 g) was added to the reaction mixture and the mixture was filtered while hot. The insoluble filter cake was thoroughly washed with hot EtOH. The EtOH was removed from the combined filtrate *in vacuo*. The separated crystals were collected to give crude **6c-6** (0.5 g), which was recrystallized.

In these procedures, epimerization did not observed and the results are summarized in Table I.

Optical Resolution of *cis*-1-Benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene (6c-1)——*cis*-1-Benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene (**6c-1**) (118 g) in EtOH (200 ml) and O,O-dibenzoyl-*d*-tartaric acid (151 g) in EtOH (200 ml) was mixed and H_2O (200 ml) was added. The solution was concentrated until crystals began to precipitate and allowed to stand at room temperature. The precipitates were collected by filtration and recrystallized six times from EtOH–H_2O, resulting in the formation of 56.5 g of the salt showing $[\alpha]_D^{20}$ −146.7° (c=1.42, EtOH). The crystals, obtained from the mother liquor, were recrystallized once from EtOH–H_2O to give 45.5 g of the another salt showing $[\alpha]_D^{20}$ +26.55° (c=1.78, EtOH). After the addition of K_2CO_3 to the suspention of the former crystals (50 g) in H_2O (100 ml) with stirring, the mixture was extracted three times with 100 ml portions of ether. The extract was dried over anhyd. Na_2SO_4, evaporated to dryness, the residue was treated with EtOH–HCl, and then the solvent was distilled off. Recrystallization of the residue from EtOH–ether gave 20.2 g of *l-cis*-1-benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene hydrochloride (*l*-**6c-1** hydrochloride) having a melting point of 211—212°, $[\alpha]_D^{20}$ −175.3° (c=1.09, EtOH). The same treatment of the latter crystals (45.5 g) as above gave 16.55 g of *d-cis*-1-benzoyloxy-2-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene hydrochloride (*d*-**6c-1** hydrochloride) having a melting point of 210—211° $[\alpha]_D^{20}$ +177.2° (c=1.73, EtOH).

1-N,N-Dimethylamino-2-tetralol (10)——*trans*-2-Bromo-1-tetralol (**9**) was prepared from *trans*-1,2-dibromo-1,2,3,4-tetrahydronaphthalene[12] according to the method of von Braun, *et al.*[12a,13]

Procedures of von Braun, *et al.*,[8a] Gonzalez, *et al.*[8b] and Straus, *et al.*,[8c] were followed to prepare 1-N,N-dimethylamino-2-tetralol (**10**), bp 158—160° (15 mmHg) [lit. bp 157—158° (13 mmHg),[8b] bp 170—171° (20 mmHg)[8c]]. Mass Spectrum *m/e*: 191 (M^+); NMR δ: 2.50 (6H, s, N–$CH_3\times2$), 1.60—2.94 (4H, m, C-3 and C-4 H), 3.20 (1H, s, OH), 3.62 (1H, d, J=9 Hz, C-1H), 3.70—3.95 (1H, m, C-2H), 6.90—7.50 (4H, m, aryl H).

Benzoyl and *p*-Nitrobenzoyl Esters of 10 (11a, 11b)——The method A described for the preparation of **6** was used to prepare **11a** and **11b**.

trans-2-Benzoyloxy-1-N,N-dimethylamino-1,2,3,4-tetrahydronaphthalene hydrochloride (**11a** hydrochloride): mp 178—180° (from EtOH–ether) (lit.[8b] mp 176°).

trans-N,N-Dimethylamino-2-(*p*-nitrobenzoyloxy)-1,2,3,4-tetrahydronaphthalene (**11b**): mp 110.5—111.5° (from benzene–petroleum ether) (lit.[8a] mp 112°).

***trans*-1-Benzyloxy-2-bromo-1,2,3,4-tetrahydronaphthalene (12d)**[14]——A mixture of *trans*-1,2-dibromo-1,2,3,4-tetrahydronaphthalene (50 g) and benzyl alcohol (250 ml) was heated at 95—100° for 3 hr. After cooling, benzyl alcohol was distilled off *in vacuo* and the oily residue (50 g) was distilled to give 25 g of **12d**. bp 150—160° (0.1—0.2 mmHg). Mass Spectrum *m/e*: 316 (M^+) was not detected. NMR δ: 1.95—3.3 (4H, m, C-3 and C-4H), 4.55—4.80 (4H, C-1 and C-2H, C_6H_5–C<u>H</u>$_2$), 7.00—7.60 (9H, aryl H).

Tetrahydropyranyl Derivative 9 (12e)——A mixture of **9** (3.3 g) and dihydropyran (1.8 g) and a small amount of *p*-toluenesulfonic acid was stirred at room temperature for 2 days. The reaction mixture was poured with stirring onto ice-water containing K_2CO_3 (2 g) and extracted with CH_2Cl_2. The extract was dried over anhyd. K_2CO_3 and evaporated under reduced pressure to give an oily dihydropyranyl derivative (**12e**) (4.3 g), which was found to be a mixture of the epimers (ratio=1: 1.2) on the basis of NMR spectrum and used without further purification.

One of the epimer of **12e** was isolated as follows when **12e** was attempted to react with dimethylamine at room temperature. A solution of **12e** (0.5 g) in a mixture of MeOH (1.5 ml), H_2O (0.5 ml) and 40% dimeth-

12) *a*) J. von Braun and G. Kirschbaum, *Chem. Ber.*, **54**, 597 (1921); *b*) T. Fujita, *J. Am. Chem. Soc.*, **79**, 2471 (1957); *c*) H.R. Buys and C.H. Leeuwestein, *Rec. Trav. Chim. Pays-Bas*, **89**, 1089 (1970).
13) Since the same 2-bromo-1-tetralol (**9**) was obtained from 1,2-dihydronaphthalene and HOBr, the configuration of **9** should be *trans*.
14) Since the reaction course seems to be the same with that of indane derivative,[6d] the configuration of **12d** should be *trans*.

ylamine (1 ml) was allowed to stand overnight at room temperature, and the precipitates were collected by filtration to give one of the epimer. mp 94°. *Anal.* Calcd. for $C_{15}H_{19}O_2Br$: C, 57.89; H, 6.15; Br, 25.67. Found: C, 57.82, H, 6.23; Br, 25.86. NMR δ: 1.0—2.0 (6H, b, O–CH–O), 2.00—3.30 (4H, m, C-3 and C-4H), 4.97 (1H, s, O–CH–O), 5.01 (1H, d, J=4 Hz, C-1H), 7.0—7.7 (4H, m, aryl H). The NMR spectrum of the oily compounds from the mother liquor showed that the ratio of the isomers was 1: 2.3. Both the crystals and the oily compound gave original bromohydrine (**9**) quantitatively, when heated at 70—80° for 5 min in a mixture of MeOH and 10% HCl.

Reaction of 12d with Dimethylamine——1) A mixture of **12d** (3 g), anhyd. dimethylamine (20 ml) and benzene (4 ml) was heated at 90—100° for 40 hr in a seealed tube. The reaction mixture was treated with Na_2CO_3 solution and extracted with ether. The organic layer was washed with H_2O, and 1N HCl, dried over anhyd. $MgSO_4$, and evaporated *in vacuo* to give 1.7 g of a mixture of solid and oil (neutral fraction). The neutral fraction was found to be a mixture of naphthalene, benzyl alcohol and an unknown compound (ratio 1: 0.7: 0.1) by the analysis of the data of GC–Mass and GC using a column DEXSIL 300 GC and OV-17 respectively. The above 1N HCl washing was made alkaline with Na_2CO_3 and extracted with ether. The extract was dried over anhyd. K_2CO_3 and evaporated *in vacuo* to give oily **13d**, 551 mg (21.3%). Distillation under reduced pressure gave pure **13d**. NMR δ: 1.6—3.4 (4H, b, C-3 and C-4H), 2.45 (3H, s, N–CH_3 × 2), 4.58 (2H, AB type quartet, J=12 Hz, C_6H_5–$C\underline{H}_2$), 7.0—7.6 (9H, m, aryl H).

2) A mixture of **12d** (1 g), 40% aqueous dimethylamine (10 ml) and EtOH (5 ml) was heated at 150° for 20 hr in a seald tube. The same treatment of the reaction mixture as above, gave **13d** (185 mg, 21.6%) and the neutral fraction (0.49 g).

3) A mixture of **12d** (2 g), anhyd. dimethylamine (12 ml) and EtOH (4 ml) was heated at 150° for 20 hr in a seald tube. The same treatment of the reaction mixture as the procedure (1) gave **13d** (473 mg, 27.4%) and the neutral fraction (0.96 g).

Hydrogenolysis of 13d——A mixture of **13d** (130 mg), AcOH (5 ml) and 10% Pd-C (20 mg) was stirred under atomospheric hydrogen pressure for 5 hr. The catalyst was filtered off, the filtrate was evaporated under reduced pressure, treated with aqueous K_2CO_3 and extracted with CH_2Cl_2. The extract was dried over anhyd. K_2CO_3 and evaporated *in vacuo* to give 40 mg of *cis*-2-N,N-dimethylamino-1-tetralol (**4c**) whose NMR spectrum was identical with that of an authentic sample.

Reaction of 12e[15] **with Dimethylamine**——A mixture of **12e** (0.5 g), 40% aqueous dimethylamine (2 ml) and MeOH (2 ml) was heated at 95—100° for 20 hr in a sealed tube. The reaction mixture was extracted with CH_2Cl_2 and the extract was mixed with 1N HCl. The organic layer was separated, dried over anhyd. $MgSO_4$, and evaporated to give a semi-solid (neutral fraction) (91 mg). The NMR spectrum showed this to be a mixture of naphthalene and dihydropyran or its decomposition product. The 1N HCl layer was made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The extract was dried over anhyd. K_2CO_3, evaporated *in vacuo* to give 120 mg of *cis*-2-N,N-dimethylamino-1-tetralol (**4c**) whose NMR spectrum was identical with that of an authentic sample.

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15) A mixture of the epimers was used.