EtOH (400 ml), the reaction mixture was clarified by suction filtration, the cake was washed with 65% aq. EtOH (200 ml), and the combined filtrate and washing were concentrated *in vacuo* bellw 45°. The residual powder was crystallized from EtOH to give yellow needles (1.0 g, mp 225—233°). Yield 76%. IR cm^{-1} (KBr): $\nu_{P=O}$ 1310, $\nu_{C=O}$ 1700. Calcd. for $C_{12}H_8O_8P$: C, 46.17; H, 2.88; P, 9.98. Found: C, 46.23; H, 3.00; P, 9.74. The NMR data are shown in Table III.

Preparation of I by Methylation of VI with CH_2N_2——A CH_2N_2-saturated ether solution (5 ml) was added to VI (90 mg) dissolved in MeOH (3 ml). On addition, vigorous generation of N_2 was observed. The mixture was allowed to stand at room temperature for 1 hr, concentrated, and the crystalline residue was recrystallized from iso-PrOH to give prisms (60 mg, mp 155—156°). Yield 73%. No mp deprssion was seen in admixture test with I prepared from VII and $(CH_3O)_2POCl$. The IR and NMR spectral patterns were identical with those of I from VII.

Hydrolysis of VI to VII——A mixture of VI (0.55 g), concentrated HCl (2 ml), and MeOH (6 ml) was refluxed for 4 hr, concentrated to dryness *in vacuo*, and the residue was recrystallized from 70% aq. EtOH to give crystals (0.33 g, mp 208—210°). Yield 81%. The IR spectral pattern was identical with that of VII prepared from VIII.

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Tetrahydronaphthylamines and Related Compounds. II.[1] Synthesis of 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-phenyl-2-naphthylamine[2]

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In our synthetic studies on analgetics, we attempted to prepare several compounds which have a bulky substituent at the 2-position of 1,2,3,4-tetrahydro-2-naphthylamine, because it is considered that their conformation will be similar to that of morphine and benzomorphan. The present paper describes the synthesis of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-phenyl-2-naphthylamine (I) and an interesting observation on stereochemistry of an amino alcohol in the course of this synthesis.

3-(3,4-Dimethoxyphenyl)-propiophenone (II)[4] was submitted to a modified Strecker reaction[5] to give the corresponding amino nitrile (III) in about 50% yield. The intramolecular cyclization of III was achieved in concentrated sulfuric acid[6] to afford 2-amino-3,4-dihydro-6,7-dimethoxy-2-phenyl-1(2H)-naphthalenone (IVa), which was methylated to give the corresponding 2-dimethylamino derivative (IVb). Attempts to reduce directly the amino ketones (IVa and IVb), *i.e.*, Wolff–Kishner reduction, Clemmensen reduction and catalytic hydrogenation, were unsuccessful. Reduction of IVa with sodium borohydride in ethanol

1) *a*) Part I: K. Mitsuhashi, J. Adachi, N. Shimizu, K. Nomura, and S. Shiotani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1321 (1972); *b*) This paper forms Part XVI of "Studies on Structure-Activity Relationship of Analgetics;" Part XV: S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1980 (1972).

2) This work was presented at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, Apr. 1972.

3) Location: *Gofuku 3190, Toyama.*

4) J. Koo, *J. Am. Chem. Soc.*, **75**, 2000 (1953).

5) R.E. Steiger, *Org. Syn.*, Coll. Vol. **III**, 586 (1955).

6) C.K. Bradsher, E.D. Little, and D.J. Beavers, *J. Am. Chem. Soc.*, **78**, 2153 (1956).

gave the amino alcohol (Va) in 82% yield. Treatment of Va with a large excess of lithium aluminum hydride–aluminum chloride (molecular ratio of 1: 3)[7] in ether afforded the desired amine (I), another amino alcohol (VIa) and dihydronaphthalene derivative (VII) in 21%, 10% and 47% yield, respectively. From spectral data and elemental analysis, it was assumed that V a would be an isomer of Va concerning the configuration of hydroxyl group. A Clarke–Eschweiler methylation of Va afforded two isomeric dimethylamino alcohols (Vb and VIb). In infrared (IR) spectra of Vb and VIb absorption bands of hydroxyl groups were shown at 3520 and 3280 (broad) cm^{-1} respectively, and the latter would probably indicate a hydrogen bonding. The compound (Vb) was also obtained by the reduction of IVb with sodium borohydride. On the basis of these data, the amino alcohols (Va, b and VIa, b) were deduced to be *trans* and *cis* isomers,[8] respectively. Furthermore, the stereochemistry of these amino alcohols were confirmed by the following chemical evidences. The amino alcohol (Va or VIa) was submitted to react with equimolar amount of aldehyde (formalin or benzaldehyde) in methanol at room temperature.[9] In the case of Va, although the reaction with formalin gave an unidentified mixture, the reaction with benzaldehyde afforded a Schiff's base (VIII). On the other hand, both of the reactions of VIa with formalin and benzaldehyde resulted in formation of the oxazolidine derivatives (IX and X). X exhibited on nuclear magnetic resonance (NMR) spectrum four singlets at 3.95 (1/2H), 4.45 (1/2H) and 4.80 (1/2H), 4.85 τ (1/2H) which were assigned to C–2 and C–5 methine protons of the oxazolidine ring respectively. This fact suggested that X would be a 1:1 mixture of stereoisomers due to configuration

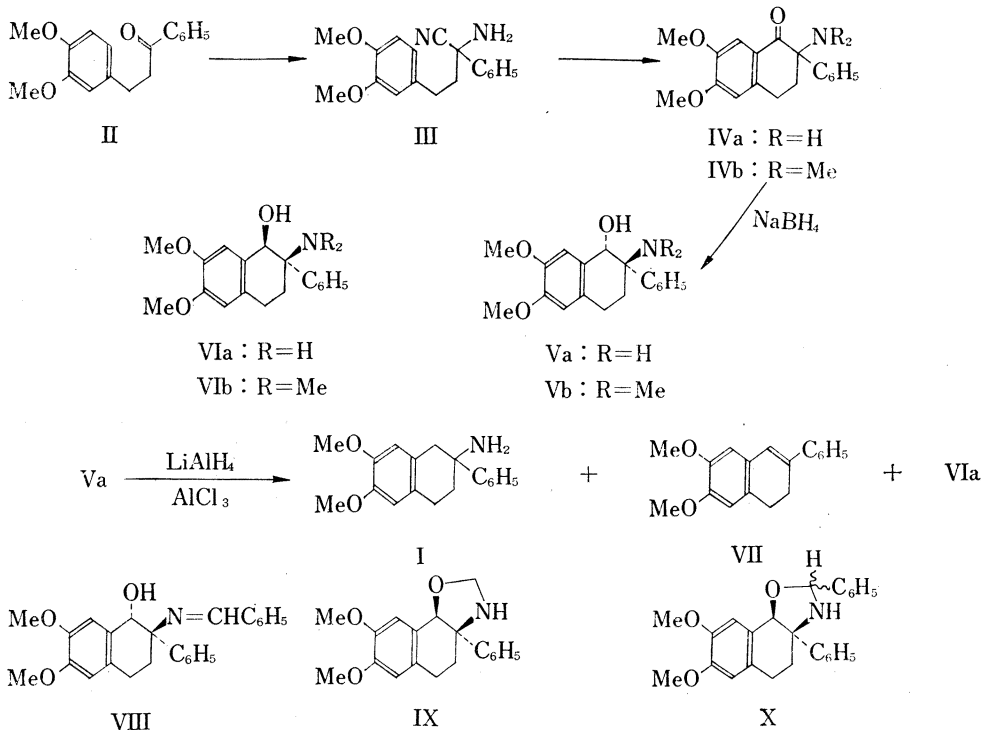


Chart 1

7) B.R. Brown and A.M.S. White, *J. Chem. Soc.*, **1957**, 3755; R.F. Nystrom and C.R.A. Berger, *J. Am. Chem. Soc.*, **80**, 2896 (1958).
8) Heteroatom substituents.
9) L. Neelakantan, *J. Org. Chem.*, **36**, 2256 (1971).

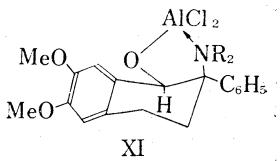
Table I. Inversion Reactions of Amino Alcohols

Compound	Reagent (s)	Solvent[a]	Time (hr)	Ratio of products (*trans*:*cis*)	Yield of product (s) (%)
Va (*trans*)	HCl	dioxane	2	2:3[b]	84
Vb (*trans*)	HCl	dioxane	2	1:1[c]	92
VIa (*cis*)	HCl	dioxane	2	1:2[b]	96
VIb (*cis*)	HCl	dioxane	2	unidentified	—
Va (*trans*)	$AlCl_3$	ether	3	1:1[b]	84
Vb (*trans*)	$AlCl_3$	ether	3	1:1[c]	83
VIa (*cis*)	$AlCl_3$	ether	3	—:1	96
Va (*trans*)	$AlCl_3$ Al_2O_3	ether	3	—:1	88
Vb (*trans*)	$AlCl_3$ Al_2O_3	ether	3	—:1	80

a) These solvents were used at reflux temperatures.
b) These ratios were determined by integration of singlets at 5.45 and 5.1τ in NMR spectra.
c) These ratios were determined in the similar manner as above (singlets at 4.7 and 4.85τ).

of C–2 of the oxazolidine ring. As a result, it is considered that sodium borohydride reduction of the amino ketone gives *trans*-amino alcohol. This observation is resemble the facts reported by Stevens, *et al.*[10] on α-aminocyclohexanone systems.

It was considered that the amino alcohol would isomerize in the presence of formic acid or aluminum chloride, because *trans*-amino alcohol (Va) yielded a mixture of *trans*- and *cis*-dimethylamino alcohol (Vb and VIb) on Clarke–Eschweiler methylation and *cis*-isomer (VIa) on reduction with a mixed hydride. So, we investigated the conversion of amino alcohol using hydrogen chloride (instead of formic acid) and aluminum chloride. These results were summerized in Table I. Treatment of *trans*-isomer (Va or Vb) with hydrogen chloride in dioxane resulted in partial conversion to *cis*-isomer as expected. Although *cis*-isomer (VIa) gave a similar mixture of *trans-cis* on treatment in the same manner as above, *cis*-dimethylamino alcohol (VIb) afforded not any mixture of *trans-cis* but an unidentified mixture which contained non-basic materials mainly. In these reactions, hydroxyl group is probably protonated and the subsequent dehydration will occur to form a carbonium ion, which will be followed by nucleophilic attack with water. On the other hand, although both of the treatments of *trans*-isomers (Va and Vb) with aluminum chloride in ether gave the corresponding mixture of *trans-cis*, similar treatment of *cis*-isomer (VIa) resulted in recovery of VIa. Treatments of *trans*-isomers (Va and Vb) with aluminum chloride–alumina yielded only the corresponding *cis*-isomers. On the basis of above observations, the formation of *cis*-isomer from *trans*-isomer in the presence of aluminum chloride can be envisaged as proceeding through a stable intermediate (XI) of which formation will be due to a fission of C–O bond. It is considered that the role of alumina will be neutralization of hydrogen chloride formed during these reactions.



XI

R=H, Me

Experimental

Melting points were determined with a Yanagimoto Micro Melting Point Apparatus and uncorrected. All boiling points were indicated by bath temperatures. NMR spectra were taken on a JNM-C-60H spectrometer, and tetramethylsilane was used as an internal standard.

10) C.L. Stevens, H.T. Hanson, and K.G. Taylor, *J. Am. Chem. Soc.*, **88**, 2769 (1966); C.L. Stevens, A.B. Ash, A. Thuillier, J.H. Amin, A. Balys, W.E. Dennis, J.P. Dickerson, R.P. Glinski, H.T. Hanson, M.D. Pillai, and J.W. Stoddard, *J. Org. Chem.* **31**, 2593 (1966).

2-Amino-3,4-dihydro-6,7-dimethoxy-2-phenyl-1(2H)-naphthalenone (IVa)——To a stirred mixture of NaCN (1.2 g), NH_4Cl (1.4 g), 28% aq. ammonia (6 ml) and water (7.5 ml) was added dropwise a solution of II[4] (5 g) in EtOH (15 ml). The reaction mixture was then kept at 60° for 4 hr and extracted with ether. The ether solution was thoroughly extracted with 5% HCl. The aqueous layer was made alkaline with K_2CO_3 and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 2.4 g of a pale yellow crystalline mass of III, mp 78—80°. Recrystallization or distillation of III resulted in partial conversion to the starting material (II). IR ν_{max}^{KBr} cm^{-1}: 3360, 3300 (NH_2), 2220 (CN).

To previously cooled (−5°) concd. H_2SO_4 (80 ml) was added III (5.5 g), and the mixture was stirred until a clear solution was obtained. The solution was then allowed to stand at room temperature for 2 days. After dilution with ice-cooled water, the reaction mixture was neutralized with K_2CO_3 and extracted with ether. The extract was worked up as usual to give colorless crystals. Recrystallization from EtOH afforded colorless cubes of IVa, mp 132—134°. Yield, 4.8 g (87%, based on II). IR ν_{max}^{KBr} cm^{-1}: 3340, 3280 (NH_2), 1660 (C=O). *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.72; H, 6.39; N, 4.51.

3,4-Dihydro-6,7-dimethoxy-2-(dimethylamino)-2-phenyl-1(2H)-naphthalenone (IVb)——A mixture of IVa (500 mg), HCOOH (5 ml) and 37% formalin (5 ml) was heated on a steam bath for 1 hr. After dilution with water, the solution was washed with ether, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was worked up as usual to give 400 mg (79%) of IVb as colorless needles, mp 96—97° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 2840, 2800 (NMe_2), 1670 (C=O).

Hydrochloride of IVb: Prepared as usual and recrystallized from ether–EtOH, mp 228—231°. *Anal.* Calcd. for $C_{20}H_{23}O_3N \cdot HCl$: C, 66.54; H, 6.70; N, 3.88. Found: C, 66.31; H, 6.63; N, 3.66.

***trans*-2-Amino-1,2,3,4-tetrahydro-6,7-dimethoxy-2-phenyl-1-naphthol (Va)**——To a solution of IVa (500 mg) in EtOH (15 ml) was added $NaBH_4$ (1.25 g), and the reaction mixture was stirred at room temperature for 3 hr. The mixture was diluted with four times volumes of water and extracted with ether. A usual working-up of the extract gave crystalline residue, which was recrystallized from EtOH to yield colorless cubes of Va, mp 150—152°. Yield, 410 mg (82%). IR ν_{max}^{KBr} cm^{-1}: 3300, 3260 (NH_2), 3140 (OH). NMR ($CDCl_3$) τ: 2.25—2.75 (5H, m, arom. protons), 3.05 (1H, s, arom. proton), 3.30 (1H, s, arom. proton), 5.45 (1H, s, >CH-O-), 6.15 (6H, s, -OCH_3), 6.9—7.4 (6H, m, -CH_2-CH_2- and -NH_2). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 71.96; H, 6.92; N, 4.38.

1,2,3,4-Tetrahydro-6,7-dimethoxy-*trans*-2-(dimethylamino)-2-phenyl-1-naphthol (Vb)——By the same procedure as above, IVb (150 mg) was treated with $NaBH_4$ (1 g) to give 140 mg (85%) of colorless cubes melting at 150—151.5° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 2840, 2780 (NMe_2). NMR ($CDCl_3$) τ: 4.7 (1H, s, >CH-O-), 6.9—7.8 (5H, m, -CH_2-CH_2- and -OH), 7.9 (6H, s, -$N(CH_3)_2$). *Anal.* Calcd. for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.16; H, 7.54; N, 4.50.

Clarke–Eschweiler Methylation of Va——A mixture of Va (200 mg), HCOOH (4 ml) and 37% formalin (4 ml) was heated on a steam bath for 9 hr. The mixture was diluted with water, made alkaline with K_2CO_3 and extracted with ether. Usual working-up of the extract gave 153 mg (70%) of a crystalline product. It turned out by NMR spectrum that this product was constituted with a mixture of Vb and VIb in a ratio of 1 : 3.

Reduction of Va with $LiAlH_4$-$AlCl_3$——To a stirred mixture of Va (100 mg) and $LiAlH_4$ (33 mg) in ether (12 ml) was added portionwise $AlCl_3$ (166 mg) maintaining gentle refluxing, and the mixture was refluxed for 6 hr. After the addition of saturated aq. potassium sodium tartrate, the products were extracted with ether. The extract was shaken with 5% HCl to obtain the basic products. A usual working-up of the ether layer gave 42 mg (47%) of VII, mp 97—98° (EtOH). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.29; H, 6.85.

The aqueous layer was made alkaline with K_2CO_3 and extracted with ether. After evaporation of the solvent, the residue was chromatographed on Al_2O_3 ("Woelm" neutral). Elution with benzene gave 20 mg (21%) of I as a colorless oil, bp 130° (10^{-5} mmHg). IR ν_{max}^{film} cm^{-1}: 3280, 3240 (NH_2). NMR ($CDCl_3$) τ: 2.2—2.8 (5H, m, arom. protons), 3.35 (2H, s, arom. protons), 6.12 (3H, s, -OCH_3), 6.15 (3H, s, -OCH_3), 6.5—7.4 (4H, m), 7.7—8.1 (2H, m), 8.0 (2H, br. s, -NH_2). *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.49; N, 4.94. Found: C, 76.12; H, 7.36; N, 4.85.

Further elution with $CHCl_3$ yielded 10 mg (10%) of VIa melting at 167—170° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3300, 3240 (NH_2), 3160 (OH). NMR ($CDCl_3$) τ: 2.3—2.8 (5H, m, arom. protons), 2.85 (1H, s, arom. proton), 3.45 (1H, s, arom. proton), 5.1 (1H, s, >CH-O-), 6.1 (3H, s, -OCH_3), 6.15 (3H, s, -OCH_3), 6.9—8.0 (6H, m, -CH_2-CH_2-, -NH_2). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.21; H, 7.03; N, 4.59.

Reactions of Amino Alcohols with Aldehydes——(A) Va with Benzaldehyde: Formation of the Schiff's Base (VIII): A solution of Va (50 mg) and benzaldehyde (18 mg) in MeOH (10 ml) was stirred at room temperature for 6 hr. After evaporation of the solvent, the residue was dissolved in ether and washed with 10% $NaHSO_3$ and water. Ether solution was dried over Na_2SO_4, and concentrated to give a colorless oil which crystallized on standing. Recrystallization from EtOH afforded 52 mg (82.5%) of colorless needles of VIII, mp 85—88°. IR ν_{max}^{film} cm^{-1}: 3240 (OH), 1640 (C=N). NMR ($CDCl_3$) τ: 1.7 (1H, s, -N=CH-), 4.8

(1H, s, >CH-O-). *Anal.* Calcd. for $C_{25}H_{25}O_3N$: C, 77.49; H, 6.50; N, 3.62. Found: C, 77.31; H, 6.50; N, 3.63.

(B) VIa with Formalin: Formation of Oxazolidine (IX): A solution of VIa (150 mg) and 37% formalin (60 mg) in MeOH (10 ml) was stirred at room temperature for 3 hr. The solvent was removed *in vacuo*, and the residue was dissolved in ether, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was distilled to yield 145 mg (71.5%) of a colorless oil of IX, bp 150° (10^{-5} mmHg). NMR ($CDCl_3$) τ: 5.17 (1H, s, >CH-O-), 5.18 and 5.42 (2H, AB-q, $J=6$ Hz), 6.95 (1H, br. s, -NH-). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.38; H, 6.70; N, 4.51.

(C) VIa with Benzaldehyde: Formation of Oxazolidine (X): A solution of VIa (50 mg) and benzaldehyde (18 mg) in MeOH (10 ml) was stirred at room temperature for 6 hr. The reaction mixture was worked up in the same manner as above (procedure (A)) to give 49 mg (78%) of X as a colorless oil, bp 150° (10^{-5} mmHg). NMR ($CDCl_3$) τ: 3.95 and 4.45 (1H, 2s, $\underset{-NH}{\overset{-O}{>}}CH-$), 4.8 and 4.85 (1H, 2s, >CH-O-), 6.9 (1H, br. p, -NH-). *Anal.* Calcd. for $C_{25}H_{25}O_3N$: C, 77.49; H, 6.50; N, 3.62. Found: C, 77.52; H, 6.35; N, 3.77.

Inversion Reactions of Amino Alcohols (see Table I)——(A) Dry HCl was saturated in dioxane (2 ml) at room temperature, and to this solution was added 50 mg of amino alcohol (Va, Vb, VIa or VIb) and refluxed for 2 hr. After removement of the solvent *in vacuo*, the residue was dissolved in water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated. The crystalline residue was recrystallized from EtOH. Yield: from Va, 42 mg of Va and VIa; from Vb, 46 mg of Vb and VIb; from VIa, 48 mg of Va and VIa; from VIb, 42 mg of an unidentified mixture.

(B) A mixture of amino alcohol (Va, Vb, or VIa) (50 mg) and $AlCl_3$ (100 mg) in ether (6 ml) was refluxed for 3 hr. After addition of water, the mixture was made alkaline with K_2CO_3 and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and concentrated to give a crystalline mass which was recrystallized from EtOH. Yield: from Va, 42 mg of Va and VIa; from Vb, 42 mg of Vb and VIb; from VIa, 48 mg of VIa (recovery).

(C) Formation of *cis*-Amino Alcohols (VIa and VIb): i) To a solution of Va (100 mg) in ether (10 ml) was added portionwise $AlCl_3$ (166 mg) followed basic Al_2O_3 (50 mg) at room temperature. After the addition was completed, the mixture was refluxed for 3 hr. To the reaction mixture was added water, made alkaline with K_2CO_3 and extracted with ether. The extract was worked up as usual to give a crystalline mass. Recrystallization from EtOH afforded 88 mg (88%) of colorless needles of VIa, mp 167—170°. This product was identified by the comparisons of IR and NMR spectra with the corresponding product obtained in the reduction of Va with $LiAlH_4$-$AlCl_3$.

ii) According to the same procedure as above, treatment of Vb (50 mg) with $AlCl_3$ (83 mg) and Al_2O_3 (25 mg) yielded 40 mg (80%) of VIb, mp 187—188° (benzene). IR ν_{max}^{KBr} cm^{-1}: 3280 (OH), 2840, 2800 (NMe_2). NMR ($CDCl_3$) τ: 4.85 (1H, s, >CH-O-), 5.65 (1H, br. s, -OH), 7.80 (6H, s, $-N(CH_3)_2$). *Anal.* Calcd. for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.10; H, 7.50; N, 4.19.

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