Notes

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Syntheses of 1,2,3,4-Tetrahydro-2-naphthylamine Derivatives[1]

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In connection with our studies on structure-activity relationship of analgetics, we were interested in the synthesis of 1,2,3,4-tetrahydro-2-naphthylamine derivatives which constitute a moiety of benzomorphan. We attempted to synthesize five compounds in order to obtain a clue of relationship between structure and analgetic activity.

A Stobbe condensation of veratraldehyde (I) with diethyl succinate gave 2-(3,4-dimethoxybenzal)-succinic acid (II), which was then catalytically hydrogenated over Raney-nickel to give the dimethoxybenzyl derivative (IIIa). The intramolecular cyclization of IIIa will be able to occur at two different positions. So we protected 6-position of the aromatic ring of IIIa by bromination in order to prevent undesirable cyclization.[3] The brominated dicarboxylic acid (IIIb) was derived to the corresponding acid anhydride with acetyl chloride, which was submitted to a Friedel-Crafts reaction to give 8-bromo-1,2,3,4-tetrahydro-5-hydroxy-6-methoxy-4-oxo-2-naphthoic acid (IV). This result resembled a fact that aryl methyl ether at peri-position to carbonyl group is readily cleaved with aluminum chloride.[4] The tetralone (IV) was reduced by Clemmensen reaction to form the compound (Va), which was followed by reductive debromination over Raney-nickel to afford the compound (Vb). Although a Schmidt reaction of Vb was unsuccessful, this reaction of the dimethoxy derivative of Va gave the desired amino compound (VIa) successfully. The compound (VIa) was then debrominated by catalytic reduction over palladium-barium carbonate to afford 1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthylamine (VIb). N,N-Dimethylamino derivative (VIc) was obtained from VIa by Eschweiler-Clarke method and the subsequent debromination.

On the other hand, methyl 1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-oxo-2-naphthoate (VII) was prepared according to the method of Bechmann and Thomas.[5] We were attempted to convert the ketone function of VII into the methylene group by reductive desulfurization of the corresponding ethylenethioketal derivative. Reactions of VII with ethylene dithiol in the presence of borontrifluoride-etherate[6] and in the presence of hydrogen chloride[7] were investigated, but these reactions resulted in recovery of VII. The hydrogenation of VII in acetic acid containing a small amount of perchloric acid[8] over Adams platinum catalyst afforded methyl 1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-naphthoate. The ester was then hydrolyzed to the corresponding carboxylic acid (VIIIa), which was submitted to a Schmidt

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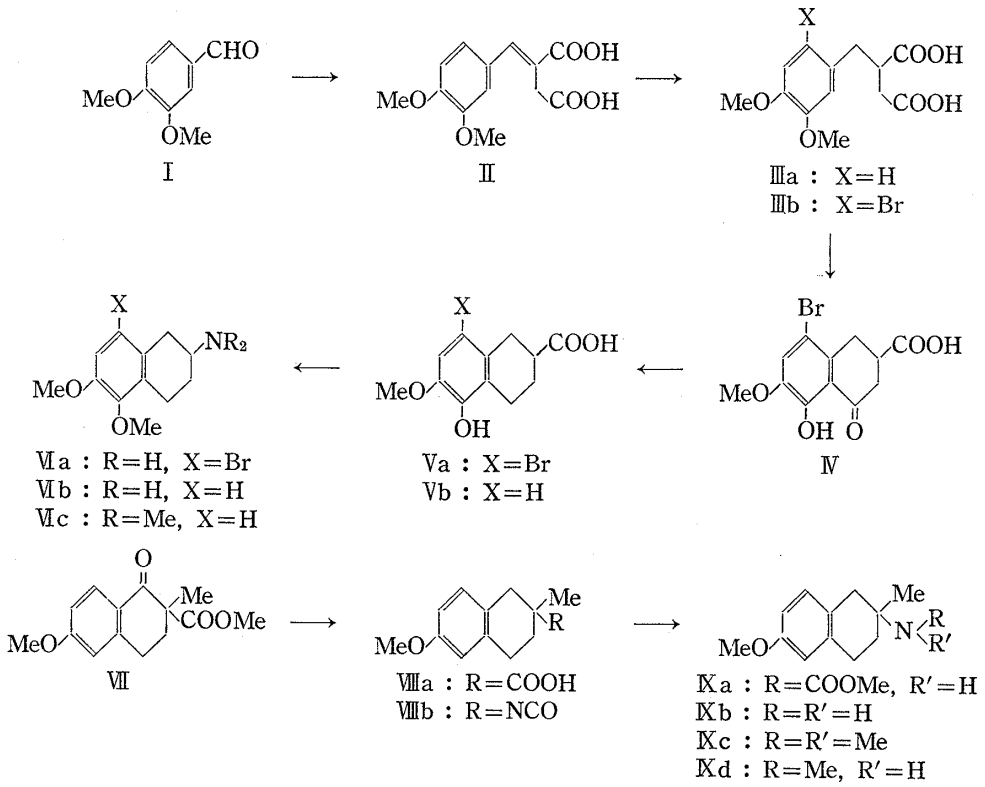
3) Z. Horii, T. Momose and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 651 (1965).
4) E. Hardegger, K. Steiner, E. Widmer and A. Pfiffner, *Helv. Chim. Acta*, **47**, 2027 (1964).
5) W.E. Bechmann and D.G. Thomas, *J. Am. Chem. Soc.*, **64**, 94 (1942).
6) L.F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).
7) J.D. Roberts, W.T. Moreland, Jr. and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953).
8) E.B. Hershberg, E. Olivto, M. Rubin, H. Staeudle and L. Kuhlen, *J. Am. Chem. Soc.*, **73**, 1144 (1951); J.T. Edward and J.M. Ferlad, *Chem. Ind.* (London), **1964**, 975.

reaction in polyphosphoric acid. However, this reaction was unsuccessful and gave only resinous material. The carboxylic acid (VIIIa) was next submitted to a Curtius reactions.[9] The acid chloride obtained from VIIIa was treated with sodium azide in toluene under refluxing for a long period (*ca.* 30 hr) to give the isocyanate (VIIIb) which was contaminated with acid azide and the starting material. When xylene was used as solvent the reaction carried out completely in a short period to give VIIIb. The compound (VIIIb) was led to the corresponding urethan (IXa) by alcoholysis with methanol. The primary amine (IXb) was obtained from VIIIb or IXa by hydrolysis with acid. The tertiary amine (IXc) was prepared by Eschweiler-Clarke methylation of IXb, and the secondary amine (IXd) was obtained from IXa by reduction with lithium aluminum hydride.[10] Further investigations of synthesis of other 2-substituted compounds related to IXb—IXd are now under progress. The pharmacological effect of these amines will be presented elsewhere.



Experimental[11]

2-(3,4-Dimethoxybenzal)-succinic Acid (II)——To a stirred solution of NaOMe in MeOH (prepared from 30 g of Na and 300 ml of MeOH) was added a mixture of I (15 g) and diethyl succinate (30 ml) under refluxing during 1 hr period, and the refluxing was continued for 4.5 hr. After addition of 300 ml of water, the mixture was refluxed for 2 hr. Most of MeOH was removed at the atmospheric pressure, then the aqueous solution was made acidic with concd. HCl. The yellow precipitate was filtered, washed with water and $CHCl_3$, and recrystallized from water to give colorless needles of II, mp 164—165°. Yield, 15 g (63%). *Anal.* Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.40; H, 5.44.

9) P.A.S. Smith, "Organic Reactions," Vol. III, John Wiley Sons, Inc., New York, N.Y., 1946, p. 337.
10) F. Wessely and W. Swoboda, *Monatsh.*, **82**, 621 (1951) [*C.A.*, **46**, 10099 (1952)].
11) Melting points were taken with a Yanagimoto Micro Melting Point Apparatus and uncorrected. All boiling points were indicated by bath temperatures. Nuclear magnetic resonance (NMR) spectra were taken on a JNM-C-60H spectrometer using TMS as an internal standard. Mass spectra were determined on a JMS-01SG double forcus high resolution spectrometer.

2-(6-Bromo-3,4-dimethoxybenzyl)-succinic Acid (IIIb)——A solution of II (15 g) in 5% NaOH (150 ml) was shaken with Raney-Ni (10 g) in an autoclave under 38 kg/cm^2 pressure of H_2 at room temperature for 5 hr. The mixture was worked up as usual to give 14 g of IIIa as colorless needles (from benzene). This product (IIIa, 12 g) was brominated with Br_2 (7.2 g) in $CHCl_3$ (100 ml) at room temperature to afford a yellow precipitate, which was recrystallized from water to give colorless needles of IIIb, mp 154—155°. Yield, 10 g (59%). *Anal.* Calcd. for $C_{13}H_{15}O_6Br$: C, 44.99; H, 4.36. Found: C, 44.79; H, 4.42.

8-Bromo-1,2,3,4-tetrahydro-5-hydroxy-6-methoxy-4-oxo-2-naphthoic Acid (IV)——A mixture of IIIb (9.7 g) and AcCl (20 ml) in $CHCl_3$ (60 ml) was refluxed on a water bath for 4 hr. The mixture was concentrated under reduced pressure to leave a crystalline residue of mp 129—130°. A solution of this product in nitrobenzene (130 ml) was added to a stirred mixture of $AlCl_3$ (15 g) and nitrobenzene (150 ml) at room temperature over a 3 hr period. The reaction mixture was then warmed at 40—60° for 2 hr. After addition of 10% HCl and removal of nitrobenzene by steam-distillation, a yellow semi-solid mass which separated from the aqueous layer was collected, and recrystallized from $CHCl_3$ and then acetone to give pale yellow cubes of IV, mp 225—227°. Yield, 3.6 g (39%). IR ν_{max}^{KBr} cm^{-1}: 3260 (broad, OH), 3100—2500 and 1720 (COOH), 1630 (C=O). *Anal.* Calcd. for $C_{12}H_{11}O_5Br$: C, 45.75; H, 3.52. Found: C, 45.71; H, 3.54.

8-Bromo-1,2,3,4-tetrahydro-5-hydroxy-6-methoxy-2-naphthoic Acid (Va)——A mixture of amalgamated Zn (prepared from mossy Zn (6.50 g), $HgCl_2$ (1.08 g) and 1% HCl (27 ml)), concd. HCl (27 ml), water (5.5 ml), AcOH (3 ml), toluene (30 ml) and IV (1.76 g) was refluxed with stirring for 5 hr. After cooling the mixture was extracted with ether, and the extract was washed with water, dried over Na_2SO_4 and then concentrated to give a crystalline mass. Recrystallization from ether–hexane afforded pale yellow prisms of Va, mp 176—177°. Yield, 1.5 g (89%). IR ν_{max}^{KBr} cm^{-1}: 3550 (OH), 3100—2500 and 1680 (COOH). Mass Spectrum: M$^+$, 300.992; $C_{12}H_{13}O_4Br$ (300.999). *Anal.* Calcd. for $C_{12}H_{13}O_4Br$: C, 47.88; H, 4.35. Found: C, 50.36; H, 4.67.

1,2,3,4-Tetrahydro-5-hydroxy-6-methoxy-2-naphthoic Acid (Vb)——A solution of Va (1.64 g) in 30% NaOH (5 ml) and MeOH (40 ml) was shaken with Raney-Ni (4 g) in H_2 atmosphere at room temperature for 5 hr. After usual working up, the product was extracted with ether. The extract was washed with water, dried over Na_2SO_4 and concentrated to give a crystalline residue. Recrystallization from acetone afforded colorless needles of Vb, mp 218—219.5°. Yield, 0.76 g (63%). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.92; H, 6.36. Found: C, 64.63; H, 6.34.

8-Bromo-1,2,3,4-tetrahydro-5,6-dimethoxy-2-naphthylamine (VIa)——To a stirred solution of Va (2 g) in 20% NaOH (2 ml) was added dropwise a mixture of Me_2SO_4 (3.5 g) and 20% NaOH (3 ml) at 30—45° over 2 hr. period, and the mixture was then heated on a water bath for 1 hr. Usual working up gave the dimethoxy derivative (1.57 g) as colorless crystals, mp 193—196° (benzene). This product (500 mg) was dissolved in $CHCl_3$ (7 ml) and concd. H_2SO_4 (1.5 ml) and then treated with NaN_3 (160 mg) at room temperature for 22 hr. After dilution with ice-water, the aqueous layer was basified with 10% NaOH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated to leave 257 mg of the crude VIa as a yellow oil. This product was used for the next step without purification. IR ν_{max}^{film} cm^{-1}: 3400—3200 (NH_2). Hydrochloride of VIa: prepared in the usual manner, mp 248—249° (MeOH–acetone). Mass Spectrum: M$^+$, 321.009; $C_{12}H_{17}O_2NBrCl$ (321.012). *Anal.* Calcd. for $C_{12}H_{16}O_2NBr \cdot HCl$: C, 44.73; H, 5.32; N, 4.35. Found: C, 45.86; H, 5.48; N, 4.34.

1,2,3,4-Tetrahydro-5,6-dimethoxy-2-naphthylamine (VIb)——A solution of VIa (0.8 g) in EtOH (30 ml) was shaken with 5% Pd-$BaCO_3$ (1 g) in H_2 atmosphere. After up-take of 75 ml of H_2, the catalyst and the solvent were removed. The residue was dissolved in water, made alkaline with NaOH and extracted with ether. The extract was worked up as usual to give the crude VIb (0.55 g) as a pale yellow oil. Treatment of VIb with HCl and ether in the usual manner and recrystallization from MeOH–ether gave colorless needles of VIb–HCl, mp 275° (slowly sublimed). *Anal.* Calcd. for $C_{12}H_{17}O_2N \cdot HCl \cdot 1/4H_2O$: C, 58.06; H, 7.51; N, 5.64. Found: C, 58.51; H, 7.36; N, 5.46.

1,2,3,4-Tetrahydro-5,6-dimethoxy-N,N-dimethyl-2-naphthylamine (VIc)——A mixture of VIa (1.11 g), HCO_2H (4 ml) and 37% formalin (3 ml) was heated on a water bath for 1.5 hr. The mixture was diluted with 10% HCl (50 ml) and filtered. The filtrate was made alkaline with K_2CO_3 and extracted with ether. After removal of the solvent the residue in EtOH (40 ml) was shaken with 5% Pd-$BaCO_3$ (2 g) under a stream of H_2 at room temperature until an up-take of 90 ml of H_2. The mixture was worked up in the similar manner as in the case of VIb to give an oily product. Distillation of the above product afforded pure VIc as a colorless oil, bp 100—110° (1 mmHg). Yield, 750 mg (82%). IR ν_{max}^{film} cm^{-1}: 2760 (NMe_2). NMR ($CDCl_3$) τ: 3.10—3.40 (2H, AB-q, J=8.9 Hz, arom. protons), 6.17 (3H, s, -OCH_3), 6.20 (3H, s, -OCH_3), 6.65—8.75 (7H, m), 7.62 (6H, s, -$N(CH_3)_2$). Hydrochloride of VIc: colorless needles, mp 220° (MeOH–acetone). *Anal.* Calcd. for $C_{14}H_{21}O_2N \cdot HCl$: C, 61.86; H, 8.61; N, 5.15. Found: C, 61.60; H, 8.52; N, 4.95.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-naphthoic Acid (VIIIa)——Methyl 1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-oxo-2-naphthoate (VII) was prepared according to the procedure of Bechmann and Thomas,[5] mp 92—93° (lit. mp 91—92.5°). A solution of VII (2.5 g) in AcOH (60 ml) and 70% $HClO_4$ (0.2 ml) was shaken with Adams platinum catalyst (125 mg) in H_2 atmosphere at room temperature for 2.5 hr. Usual working up gave 1.6 g of the crude ester as a colorless oil. This product in 10% NaOH (6 ml) and MeOH (35 ml) was refluxed on a water bath for 1 hr. After removal of MeOH *in vacuo* the aqueous solution was

acidified with HCl and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and then concentrated to afford a crystalline mass. Recrystallization from ether–hexane gave colorless sticks of VIIIa, mp 131—134°. Yield, 0.77 g (34.7%). IR ν_{max}^{KBr} cm^{-1}: 3200—2400 and 1690 (COOH). *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.69; H, 7.47.

N-Carbomethoxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-naphthylamine (IXa)——The acid (VIIIa, 490 mg) was treated with $SOCl_2$ (2 ml) at 60° for 3 hr. Removal of the excess of $SOCl_2$ *in vacuo* gave a pale yellow viscous oil, which was distilled to give the acid chloride (448 mg), bp 128—135° (0.15 mmHg). A mixture of the above product in xylene (10 ml) and NaN_3 (230 mg) was refluxed with stirring for 5 hr. After cooling, the inorganic materials were filtered off and washed with benzene. Concentration of the combined organic solution afforded 370 mg of the crude isocyanate (VIIIb) which infrared (IR) spectrum showed a strong absorption at 2250 cm^{-1}. A solution of crude VIIIb (420 mg) in MeOH (2 ml) containing a catalytic amount of LiOMe was allowed to stand overnight at room temperature. Removal of the solvent and recrystallization from ether gave colorless prisms of IXa, mp 87—89°. Yield, 290 mg (52%, based on VIIIa). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1710 (C=O). NMR ($CDCl_3$) τ: 2.95—3.45 (3H, m, arom. protons), 6.28 (3H, s, $-OCH_3$), 6.45 (3H, s, $-OCH_3$), 7.05—8.90 (7H, m), 8.65 (3H, s, $>C-CH_3$). *Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.31; H, 7.76; N, 5.81.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-naphthylamine (IXb)——a) A mixture of the crude VIIIb (200 mg, descrived in the procedure for IXa) in benzene (6 ml) and concd. HCl (2 ml) was refluxed on a water bath for 3 hr. Concentration *in vacuo* to dryness and recrystallization from MeOH–ether afforded 168 mg of colorless fine needles of IXb–HCl, mp 229—232°. *Anal.* Calcd. for $C_{12}H_{17}ON \cdot HCl$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.07; H, 7.93; N, 5.94. The free base (IXb) was obtained from the above salt in the usual manner, bp 160—180° (0.08 mmHg). IR ν_{max}^{film} cm^{-1}: 3310 and 3200 (NH_2). NMR ($CDCl_3$) τ: 2.85—3.40 (3H, m, arom. protons), 6.22 (3H, s, $-OCH_3$), 6.85—7.40 (6H, m, $-NH_2$ and 2 × benzylic $-CH_2-$), 8.00—8.45 (2H, m), 8.76 (3H, s, $>C-CH_3$).

b) A mixture of IXa (150 mg) in benzene (5 ml) and concd. HCl (1.5 ml) was refluxed for 10 hr. Working up in the same manner as above gave 86 mg (65%) of IXb–HCl, mp 229—231°. This product was identified with the product obtained in the procedure a) by a mixed melting point measurement (mp 229—232°).

1,2,3,4-Tetrahydro-6-methoxy-N,N,2-trimethyl-2-naphthylamine (IXc)——A mixture of IXb (145 mg), HCO_2H (0.2 ml) and 37% formalin (0.15 ml) was heated on a steam bath for 2 hr. After concentration *in vacuo* the syrupy residue was treated with saturated K_2CO_3 solution and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was distilled to give colorless oil of IXc, bp 125—130° (0.09 mmHg). Yield, 81 mg (50%). IR ν_{max}^{film} cm^{-1}: 2780 (NMe_2). NMR (CCl_4) τ: 3.0—3.6 (3H, m), 6.36 (3H, s, $-OCH_3$), 7.05—7.55 (4H, m), 7.86 (6H, s, $-N(CH_3)_2$), 8.15—8.65 (2H, m), 9.13 (3H, s, $>C-CH_3$). Hydrochloride of IXc: colorless needles, mp 205—209° (MeOH–acetone). *Anal.* Calcd. for $C_{14}H_{21}ON \cdot HCl$: C, 65.73; H, 8.67; N, 5.47. Found: C, 65.77; H, 8.65; N, 5.29.

1,2,3,4-Tetrahydro-6-methoxy-N,2-dimethyl-2-naphthylamine (IXd)——A solution of IXa (88 mg) in ether (5 ml) was added to a suspension of $LiAlH_4$ (11 mg) in ether (2 ml), and the mixture was stirred at room temperature for 1.5 hr. After addition of water (5 ml) and 10% K_2CO_3 (10 ml) the mixture was extracted with ether. The extract was worked up as usual to afford an oily material. Distillation gave a colorless oil of IXd, bp 115—125° (0.09 mmHg). Yield, 21 mg (29%). IR ν_{max}^{film} cm^{-1}: 3280 (NH), 2800 (NMe). NMR ($CDCl_3$) τ: 2.85—3.50 (3H, m), 6.27 (3H, s, $-OCH_3$), 7.00—7.50 (4H, m), 7.65 (3H, s, $-NH-CH_3$), 8.05—8.60 (3H, m, $-NH-Me$ and $-CH_2-$), 8.88 (3H, s, $>C-CH_3$). Picrate of IXd: yellow needles, mp 183—185° (MeOH). *Anal.* Calcd. for $C_{13}H_{19}ON \cdot C_6H_3O_7N_3$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.58; H, 5.02; N, 12.72.

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