UDC 547.655.1:615.779.931

81. Zen-ichi Horii, Ichiya Ninomiya, and Yasumitsu Tamura : Studies on Oxytetracycline and Related Compounds. XI.*1 Synthesis of Terranaphthol.

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In connection with the synthesis of terranaphthoic acid described in the preceding paper,[1] the synthesis of terranaphthol is described in this report.

Terranaphthol and terranaphthoic acid are important degradation products of oxytetracycline and play important roles in the structural study of this antibiotic. The chemical structure of terranaphthol was determined as 4,5-dihydroxy-2-hydroxymethyl-1-methylnaphthalene by Hochstein, *et al.*,[2] but its chemical synthesis has not yet been accomplished.

As a preliminary experiment, a synthetic study of 4-hydroxy-2-hydroxymethyl-1-methylnaphthalene, was selected, i.e. 5-desoxyterranaphthol, through the Hauser rearrangement[3] of 1-dimethylaminomethyl-4-methoxynaphthalene methiodide, which was easily obtainable from 4-methoxy-1-naphthaldehyde.

Finding that this synthetic route adopted gave satisfactory results for the synthesis of this model compound, the synthesis of terranaphthol was carried out with success.

4-Methoxy-1-methylaminomethylnaphthalene (Va), prepared from the reductive amination of 4-methoxy-1-naphthaldehyde in the presence of methylamine over a Raney nickel catalyst, was converted into dimethylaminomethyl derivative (VIa) according to the procedure of Eschweiler and Clarke.[4] The methiodide (VIIa) of (VIa) was subjected to the Hauser rearrangement by means of sodium amide in liquid ammonia to give 2-dimethylaminomethyl-4-methoxy-1-methylnaphthalene (VIIIa) in 87% yield. By refluxing the glacial acetic acid solution of ethobromide (Xa) of (VIIIa) and anhydrous sodium acetate, (Xa) was converted into 2-acetoxymethyl-4-methoxy-1-methylnaphthalene (XIa), which was then hydrolysed to the 2-hydroxymethyl derivative (XIIa) by heating it with hydrous ethanol solution of sodium hydroxide. Demethylation of (XIIa) to (Ia) was attempted with various demethylating agents, such as 48% hydrobromic acid, pyridine hydrochloride, or aluminum chloride, but only resinous products resulted. This attempt was abandoned and (XIIa) was instead oxidized with potassium permanganate to (XIIIa) and demethylated (XIIIa) with hydrobromic acid, giving 4-hydroxy-1-methyl-2-naphthoic acid (XIVa), which was then reduced with lithium aluminum hydride to (Ia).

Synthesis of 4,5-dihydroxy-2-hydroxymethyl-1-methylnaphthalene from 4,5-dimethoxy-1-naphthaldehyde in place of 4-methoxy-1-naphthaldehyde in the preliminary experiment was attempted. 4,5-Dimethoxy-1-naphthaldehyde, prepared by formylation of 1,8-dimethoxynaphthalene via the Vilsmeier reaction, was converted into 4,5-dimethoxy-1-methylaminomethylnaphthalene (Vb) by the catalytic reduction of (IVb) over Raney nickel in a methanolic solution of methylamine. Methylation of (Vb) with methyl iodide and potassium carbonate in methanol solution yielded 4,5-dimethoxy-1-dimethylaminomethylnaphthalene methiodide (VIIb), which was subjected to the Hauser rearrangment to give

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*1 Part X : This Bulletin, **7**, 281(1959).

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1) Z. Horii, *et al.* : This Bulletin, **5**, 284(1957); **7**, 281(1959).
2) F.A. Hochstein, *et al.* : J. Am. Chem Soc., **75**, 5455(1953).
3) S.W. Kantor, C.R. Hauser : J. Am. Chem. Soc., **73**, 4122(1951); W.R. Brasen, C.R. Hauser : J. Org. Chem., **18**, 806(1953).
4) M.L. Moore : Org. Reactions, **5**, 323(1949).

4,5-dimethoxy-2-dimethylaminomethyl-1-methylnaphthalene (VIIIb). By refluxing the glacial acetic acid solution of ethobromide (Xb) of (VIIIb) and anhydrous sodium acetate, (Xb) was converted into 2-acetoxymethyl-4,5-dimethoxy-1-methylnaphthalene (XIb), followed by hydrolysis with sodium hydroxide to provide 2-hydroxymethyl derivative (XIIb). This was shown to be identical with the dimethyl ether of terranaphthol derived from oxytetracycline, by comparison of the melting point and infrared spectrum (Fig. 1). (XIIb) was

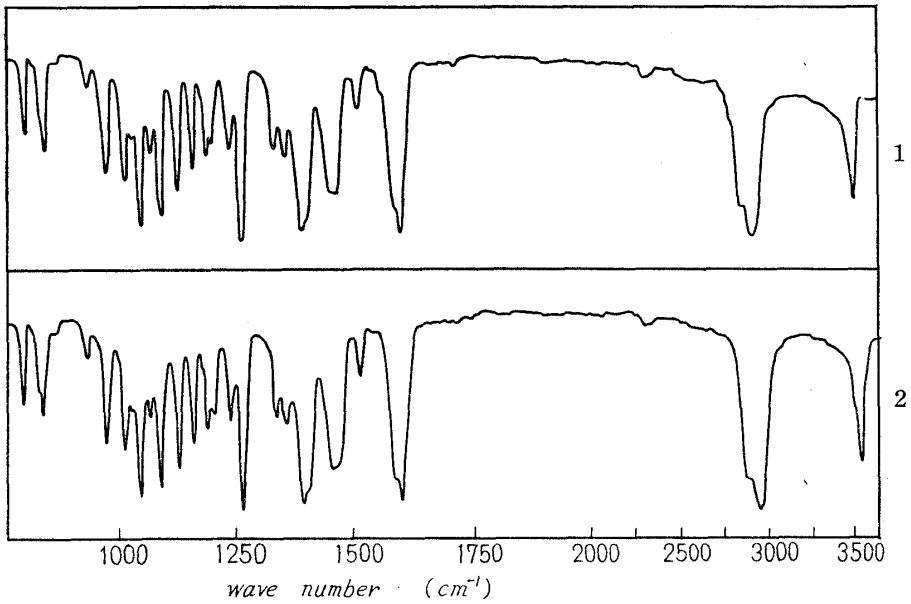


Fig. 1. Infrared Absorption Spectra of Terranaphthol Dimethyl Ether (XIIb) (in Nujol)
1. Natural 2. Synthetic

oxidized to the corresponding acid (XIIIb), followed by demethylation with hydrobromic acid to give 4,5-dihydroxy-1-methyl-2-naphthoic acid (XIVb), which was subsequently reduced with lithium aluminum hydride to 4,5-dihydroxy-2-hydroxymethyl-1-methylnaphthalene (Ib), i.e. terranaphthol.[5] Crude (Ib) was acetylated with acetic anhydride and

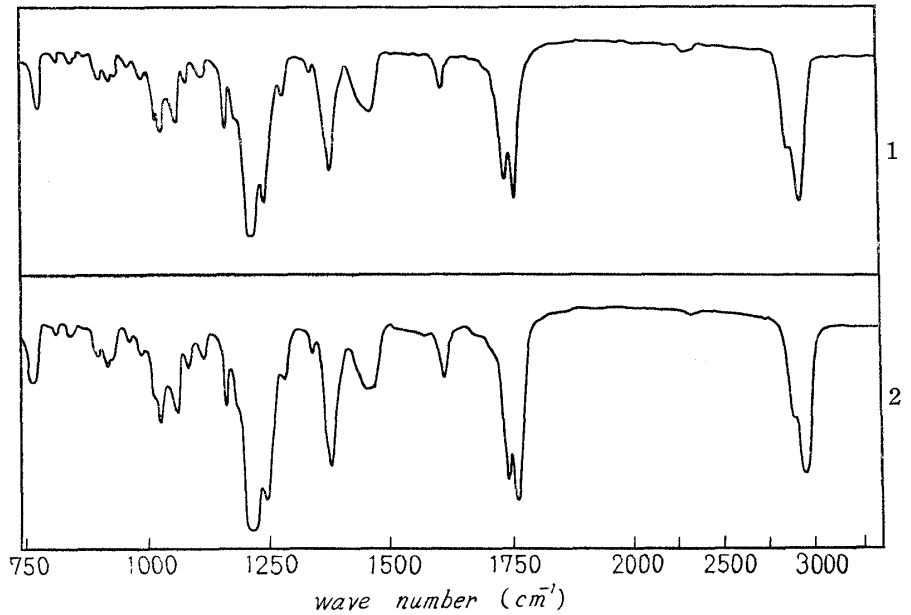
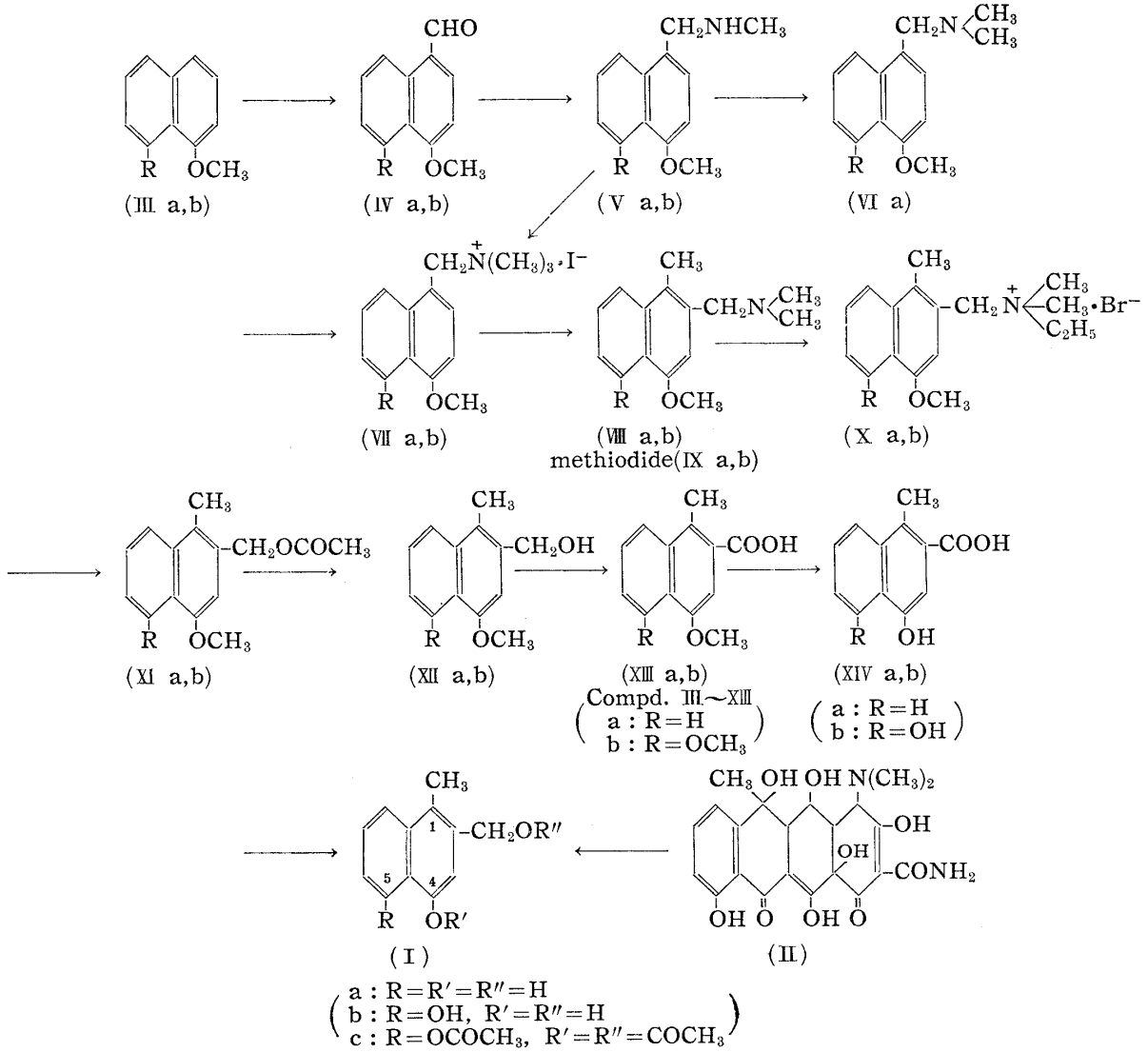


Fig. 2. Infrared Absorption Spectra of Terranaphthol Triacetate (Ic) (in Nujol)
1. Natural 2. Synthetic

5) R. Pasternack, *et al.*: J. Am. Chem. Soc., **74**, 1926(1952).

pyridine to its triacetate (Ic), m.p. 143.2~144°. The identity of the triacetate (Ic) here obtained with the triacetate[5] of terranaphthol obtained from the antibiotic (II) was established by direct comparison of the melting point and the infrared spectrum (Fig. 2).



The authors wish to thank Dr. F. A. Hochstein of the Research Laboratories of Chas. Pfizer & Co., Inc. for his kindness in supplying a sample of terranaphthol triacetate derived from oxytetracycline (II).

Experimental

(1) Synthesis of 5-Desoxyterranaphthol

4-Methoxy-1-naphthaldehyde (IVa)—Prepared from 1-methoxynaphthalene (IIIa) according to the method of Buu-Hoï.[6]

4-Methoxy-1-methylaminomethylnaphthalene (Va)—A mixture of 9.2 g. of 4-methoxy-1-naphthaldehyde (IVa), 3 g. of Raney Ni, and 300 cc. of MeOH solution of $MeNH_2$ (from 20 g. of $MeNH_2 \cdot HCl$) was shaken in a hydrogenation autoclave. Initial pressure of H_2 was 4 atm. at 10°. Hydrogen uptake started when the reaction temperature was raised to 60° and ceased within about 30 min. After shaking for an additional hr., the reaction mixture was filtered and the filtrate evaporated, giving a colorless oil which was purified by vacuum distillation, b.$p_{0.5}$ 158~163°. Yield, 8.9 g. (91%).

Hydrochloride : Colorless crystals (from EtOH-Et_2O), m.p. 234~236°. *Anal.* Calcd. for $C_{13}H_{16}ONCl$: C, 65.61; H, 6.78. Found : C, 65.75; H, 6.71.

1-Dimethylaminomethyl-4-methoxynaphthalene (VIa)—A mixture of 7 g. of (Va), 4.5 g. of 90%

6) Ng. Ph. Buu-Hoï, D. Lavit : J. Chem. Soc., **1955**, 2776.

HCOOH, and 3.5 g. of 35% HCHO was refluxed for 10 hr. The reaction solution was acidified with 1.7 cc. of conc. HCl, and then an excess of HCOOH and HCHO were removed by evaporation on a steam bath. The residual colorless oil was dissolved in water, made alkaline with 25% NaOH solution, and then steam-distilled. The distillate was saturated with KOH and an oil that separated was extracted with Et_2O. The Et_2O solution was washed with water, dried over anhyd. Na_2SO_4, and distilled, affording 7.4 g. (99%) of (VIa) as a colorless oil, $b.p_3$ 147~148°. *Anal.* Calcd. for $C_{14}H_{18}ONCl$: C, 66.80; H, 7.15. Found: C, 66.52; H, 7.40.

1-Dimethylaminomethyl-4-methoxynaphthalene Methiodide (VIIa)—To a stirred solution of 8.3 g. of (VIa) in 50 cc. of dehyd. MeOH, 20 g. of MeI was added in small portions. The mixture was refluxed for 0.5 hr. on a steam bath, cooled, and 50 cc. of Et_2O was added, thus separating a precipitate. This was collected, washed with Et_2O, and dried, giving 12.5 g. (90%) of colorless needles, m.p. 198.5~200°. *Anal.* Calcd. for $C_{15}H_{20}ONI \cdot \frac{1}{2}H_2O$: C, 49.18; H, 5.74. Found: C, 49.13; 49.44. H, 5.59; 5.71.

Rearrangement of (VIIa) to 2-Dimethylaminomethyl-4-methoxy-1-methylnaphthalene (VIIIa)—The procedure used was essentially the same as that described by Hauser[3] with the exception of shortening the reaction time.

To a suspension of $NaNH_2$ (from 1.2 g. of Na) in 200 cc. of liq. NH_3, 5.4 g. of the methiodide (VIIa) was added as rapidly as possible. The resulting mixture was stirred for 20 min. and then the unreacted $NaNH_2$ was decomposed by addition of 1 g. of NH_4Cl. After evaporation of liq. NH_3, the residue was dissolved in water and extracted with Et_2O. The Et_2O extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue, on distillation, gave a colorless oil (3.0 g., 87%), $b.p_4$ 158~160°. *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35. Found: C, 78.61; H, 8.24. Methiodide (IXa): m.p. 205~206° (decomp.), showing depression on admixture with the methiodide of (VIIa). *Anal.* Calcd. for $C_{16}H_{22}ONI$: C, 51.78; H, 5.93. Found: C, 51.60; H, 5.77.

2-Dimethylaminomethyl-4-methoxy-1-methylnaphthalene Ethobromide (Xa)—A solution of 3 g. of (VIIIa) and 10 g. of EtBr in 20 cc. of dehyd. MeOH was refluxed for 1.5 hr. on a steam bath. The unreacted EtBr and MeOH were distilled off to give 3.9 g. (87%) of crude (Xa), which was purified by recrystallization from MeOH-Et_2O to colorless needles, m.p. 179.5~181°(decomp.). *Anal.* Calcd. for $C_{17}H_{24}ONBr$: C, 60.36; H, 7.10. Found: C, 60.11; H, 6.96.

2-Acetoxymethyl-4-methoxy-1-methylnaphthalene (XIa)—A solution of 3.9 g. of the ethobromide (Xa) and 3 g. of freshly fused NaOAc in 20 cc. of glacial AcOH was heated under reflux for 30 hr. in an oil bath (150~160°). When cool, the reaction mixture was diluted with an equal volume of water, neutralized with solid $NaHCO_3$, and extracted with Et_2O. The Et_2O extract was washed successively with dil. HCl and saturated $NaHCO_3$ solution, dried over anhyd. Na_2SO_4, and the solvent was evaporated. The oily residue was distilled to give (XIa) (1.5 g., 54%) as colorless oil, $b.p_{0.1}$ 151~153°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.95; H, 6.41.

2-Hydroxymethyl-4-methoxy-1-methylnaphthalene (XIIa)—A solution of 1.4 g. of (XIa) and 0.37 g. of NaOH in 10 cc. of 30% EtOH was refluxed for 12 hr. When cool, (XIIa) separated out from the resulting solution as white crystals and recrystallized from benzene-petr. benzine to colorless needles, m.p. 80~81°. Yield, 1.1 g. (95%). *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 77.20; H, 6.98. Found: C, 77.13; H, 6.83.

4-Methoxy-1-methyl-2-naphthoic Acid (XIIIa)—A solution of 200 mg. of the foregoing carbinol (XIIa) and 0.3 g. of $KMnO_4$ in a mixture of 7 cc. of acetone and 3 cc. of water was stirred at 10° for 5 hr. The unreated permanganate was decomposed with HCHO, the inorganic salt that separated was filtered off, and washed with acetone. The filtrate and acetone washings were combined and concentrated to about 3 cc., diluted with water, neutralized with solid $NaHCO_3$, and filtered. The resulting yellow solution was acidified with conc. HCl and the white precipitate of carboxylic acid (XIIIa) was purified by recrystallization from water to colorless crystals, m.p. 162~163°. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.67; H, 5.56.

4-Hydroxy-1-methyl-2-naphthoic Acid (XIVa)—A suspension of 200 mg. of (XIIIa) in 10 cc. of 48% HBr was heated under reflux for 12 hr. in an oil bath (170°). The reaction mixture was allowed to cool to room temperature, separating a precipitate, which was recrystallized from water to form colorless needles, m.p. 202~205°(decomp.), undepressed by admixture with an authentic sample prepared according to the method of Haworth, *et al.*[7] *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.44; H, 5.04.

4-Hydroxy-2-hydroxymethyl-1-methylnaphthalene (Ia)—To a suspension of 100 mg. of $LiAlH_4$ in 10 cc. of dehyd. tetrahydrofuran, a solution of 80 mg. of (XIVa) in 10 cc. of tetrahydrofuran was added dropwise. The mixture was allowed to stand at room temperature for 2 hr. and then refluxed for 2 hr. on a steam bath. To the reaction mixture, water was added carefully to decompose an excess of $LiAlH_4$ and then the organic solvent was removed. The residual solution was diluted

7) R.D. Haworth, B. Jones, Y.M. Way, : J. Chem. Soc., **1943**, 10.

with water, acidified with dil. HCl, and extracted with Et_2O. The Et_2O extract was washed with aq. $NaHCO_3$ solution and water, dried over anhyd. Na_2SO_4, and worked up as usual. Colorless crystals (from water), m.p. 137~138°. *Anal.* Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.32; H, 6.38.

(2) Synthesis of Terranaphthol

4,5-Dimethoxy-1-naphthaldehyde (IVb)—Prepared according to the method of Buu-Hoï, *et al*,[8] $b.p_{12}$ 221°, m.p. 95°.

4,5-Dimethoxy-1-methylaminomethylnaphthalene (Vb)—Obtained in 85% yield from (IVb) by the same procedure as for (Va). Colorless oil, $b.p_{0.1}$ 160°.
Hydrochloride: Colorless crystals (from EtOH), m,p. 228~229° (decomp.). *Anal.* Calcd. for $C_{14}H_{18}O_2NCl$: C, 62.92: H, 6.74. Found: C, 62.92; H, 6.76.

4,5-Dimethoxy-1-dimethylaminomethylnaphthalene Methiodide (VIIb)—A suspension of 2 g. of (Vb), 10 g. of MeI, and 6 g. of anhyd. K_2CO_3 in dehyd. MeOH was refluxed on a steam bath for 40 hr. The precipitated methiodide (VIIb) was collected and purified from MeOH-Et_2O, forming colorless crystals, m.p. 193~194°(decomp.). Yield, about 2 g. The filtrate was evaporated to dryness, giving a small amount of crude methiodide. This was dissolved in dehyd. acetone and purified chromatographically through alumina column. *Anal.* Calcd. for $C_{16}H_{22}O_2NI$: C, 49.61; H, 5.68. Found: C, 49.30; H, 5.67.

Rearrangement of (VIIb) to 4,5-Dimethoxy-2-dimethylaminomethyl-1-methylnaphthalene (VIIIb)—To a suspension of $NaNH_2$ (from 2 g. of Na) in 200 cc. of liq. NH_3, 1 g. of the foregoing compound (VIIb) was added in portions as rapidly as possible. After stirring for 20 min., an excess of $NaNH_2$ was decomposed carefully with NH_4Cl. Liq. NH_3 was allowed to evaporate, the residue was dissolved in water and extracted with Et_2O. The Et_2O layer was separated, washed, dried, and evaporated. When cool, the residual oil solidified to colorless crystals, m.p. ca. 83~85°. Yield, 0.5 g.
Methiodide (IXb): Obtained by treating (VIIIb) with MeI giving colorless needles (from MeOH-Et_2O), m.p. 204~205°(decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_2NI$: C, 50.87; H, 5.98. Found: C, 51.39; H, 5.92.

4,5-Dimethoxy-2-dimethylaminomethyl-1-methylnaphthalene Ethobromide (Xb)—The compound (Xb) was obtained by treating (VIIIb) with EtBr. Colorless needles (from MeOH-Et_2O), m.p. 182~183° (decomp.). *Anal.* Calcd. for $C_{18}H_{26}O_2NBr$: C, 58.69; H, 7.06. Found: C, 58.37; H, 6.82.

2-Acetoxymethyl-4,5-dimethoxy-1-methylnaphthalene (XIb) and 2-Hydroxymethyl-4,5-dimethoxy-1-methylnaphthalene (XIIb)—(a) From (Xb): A mixture of 22 g. of (Xb) and 1 g. of freshly fused NaOAc dissolved in 10 cc. of glacial AcOH was refluxed for 30 hr. The reaction mixture was diluted with an equal volume of water, neutralized with solid $NaHCO_3$, and extracted with Et_2O. The Et_2O extract was washed with dil. HCl and aq. $NaHCO_3$ solution, and dried over anhyd. Na_2SO_4. The solvent was removed by distillation, leaving 0.8 g. of a brownish oily acetate (XIb), 1.4 g. of which was dissolved in a solution of 0.3 g. of NaOH in 10 cc. of 30% EtOH and this was refluxed on a steam bath for 12 hr. From the resulting solution, white crystals separated out after cooling and were recrystallized from water to colorless needles, m.p. 102°, when dried *in vacuo*. Yield, 71%. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 6.72.

(b) Methylation of Terranaphthol (Ib) prepared from Oxytetracycline (II): A suspension of terranaphthol (Ib), MeI, and anhyd. K_2CO_3 in dehyd. acetone was refluxed 90 hr. on a steam bath and the inorganic salt was filtered off. The acetone extract was evaporated to dryness and the residual paste was purified by recrystallization from hot water to give colorless needles, melting at 101~101.5° after drying *in vacuo*, which was not depressed when mixed with a sample of 2-hydroxymethyl-4,5-methoxy-1-methylnaphthalene (XIIb). *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.25; H, 6.95.

4,5-Dimethoxy-1-methyl-2-naphthoic Acid (XIIIb)—200 mg. of the foregoing carbinol (XIIb) and 0.3 g. of $KMnO_4$ were added into a solution of 7 cc. of acetone and 3 cc. of water, and the mixture was stirred for 5 hr. at 10°. An excess of $KMnO_4$ was decomposed by adding HCHO solution, the separated inorganic salts were removed by filtration, and washed thoroughly with acetone. The combined acetone extract was concentrated to ca. 3 cc., diluted with water, neutralized with solid $NaHCO_3$, and filtered. The resulting yellow solution was acidified with conc. HCl to precipitate crude crystals of the carboxylic acid (XIIIb), which were purified by recrystallization from water to form yellow crystals, m.p. 171.5~173°. *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.40; H, 5.56.

4,5-Dihydroxy-1-methyl-2-naphthoic Acid (Terranaphthoic Acid) (XIVb)—A suspension of 100 mg. of the foregoing dimethyl ether (XIIIb) in 10 cc. of 48% HBr was refluxed in an oil bath (150~170°) for 10 hr. When cool, crude crystals of (XIVb) separated out and were recrystallized from water to yellow needles, m.p. 234~235.5°(decomp.), showing no depression when mixed with a sample prepared by

8) Ng. Ph. Buu-Hoï, D. Lavit: J. Chem. Soc., **1956**, 2412.

the method reported in the preceding paper.*1 Yield, 56 mg. (45%). *Anal.* Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found : C, 66.03; H, 4.72.

4,5-Dihydroxy-2-hydroxymethyl-1-methylnaphthalene (Terranaphthol) (Ib)—Terranaphthol was obtained from 100 mg. of (XIVb) using the method described for (Ia), except that dehyd. Et_2O was used as a solvent in place of tetrahydrofuran; m.p. 170~172°. This compound (Ib) was converted to its triacetate (Ic) by treating (Ib) with a mixture of 0.2 cc. of pyridine and 0.2 cc. of Ac_2O at room temperature. The crude triacetate was recrystallized from cyclohexane, giving a slightly yellow powder of m.p. 142~143°. A sample for analysis was distilled at 0.001 mm. in an oil bath (150~200°), and recrystallized from cyclohexane to colorless crystals, m.p. 143.2~144°, showing no depression when mixed with a sample of terranaphthol triacetate, m. p. 145.5~146°, prepared from oxytetracycline (II). *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 66.44, H, 5.49. Found : C, 65.85; H, 5.50.

Summary

The structure of terranaphthol, a degradation product of oxytetracycline, was identified as 4,5-dihydroxy-2-hydroxymethyl-1-methylnaphthalene (Ib) by its synthesis through the Hauser rearrangement of 4,5-dimethoxy-1-dimethylaminomethylnaphthalene methiodide (VIIb).

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82. Shoji Shibata,*3 Izumi Imaseki,*4 and Mikio Yamazaki*3 : Phytochemical Investigation on Cultivation of Medicinal Plants. XV.*1 The Biogenesis of Ephedrine in Ephedra. (5).*2

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Previously, it was shown that *l*-ephedrine in *Ephedra distachya* L. is biosynthesized from phenylalanine using ^{15}N-labeled tracer technique,[1] and that addition of one carbon fragment occurs during the process of biosynthesis after decarboxylation of the amino acid.[2] A biological methylation with methionine(*methyl*-^{14}C) was found to form N-$^{14}CH_3$ group in ephedrine molecule.[3]

Recently, after completion of the present work, it was learned that Leete[4] obtained an evidence for the incorporation of DL-phenylalanine(3-^{14}C) into *d*-norpseudoephedrine in the leaves of *Catha edulis* FORSK., which supports these previous results.

The present paper concerns chiefly with an investigation undertaken to elucidate in detail the intermediate process of ephedrine biosynthesis.

ω-Aminoacetophenone(*carbonyl*-^{14}C) was fed to the intact Ephedra plant and the labeled ephedrine isolated from the plant was degraded to determine the location of radioactivity.

ω-Aminoacetophenone was reported as being synthesized from acetophenone by bro-

*1 Part XIV : This Bulletin, **5**, 594(1957).
*2 (4). *Ibid.*, **5**, 594(1957). cf. Chem. & Ind. (London), **1958**, 1625.
*3 Hongo, Tokyo (柴田承二, 山崎幹夫).
*4 Kamimeguro 8-chome, Meguro-ku, Tokyo (今関和泉).
1) S. Shibata, I. Imaseki : This Bulletin, **4**, 277(1956).
2) S. Shibata, I. Imaseki, M. Yamazaki : *Ibid.*, **5**, 594(1957).
3) *Idem.* : *Ibid.*, **5**, 71(1957).
4) E. Leete : Chem. &. Ind. (London), **1958**, 1088.