AcOEt extract was washed with dil. $NaHCO_3$ and H_2O, dried and evaporated to give 510 mg. of a yellow oil, which solidified spontaneously. Recrystallizations from EtOH gave colorless needles, m.p. 97°. *Anal.* Calcd. for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found : C, 61.07; H, 5.22.

Summary

The lithium aluminum hydride reduction of the half ester VIII, obtained by alcoholysis of 1,6,8-trimethoxy-2,3-naphthalenedicarboxylic anhydride (VII), afforded two kinds of lactones of m.p. 185° and m.p. 202°, among which the former lactone of m.p. 185° was shown to be identical with natural α-sorigenin dimethyl ether, and the latter lactone of m.p. 202° with 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone (X) prepared in the previous paper. Thus, the structure of α-sorigenin dimethyl ether was proved to be 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone by synthetic means.

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54. Zen-ichi Horii, Toyoshi Katagi, and Yasumitsu Tamura : Synthetic Studies on Sorigenins. VII.1) Synthesis of α-Sorigenin Dimethyl Ether (3-Hydroxymethyl-1,6,8-trimethoxy-2-naphthoic Acid γ-Lactone). (2).

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In the preceding paper,1) the structure I of α-sorigenin dimethyl ether was proved by synthetic means. That is, of both lactones obtained by the reductions of the half esters of 1,6,8-trimethoxy-2,3-naphthalenedicarboxylic acid with lithium aluminum hydride, one coincided with known 3-hydroxymethyl-4,5,7-trimethoxy-2-naphthoic acid γ-lactone2) and the other with natural α-sorigenin dimethyl ether. This report describes the synthesis of I by an alternative unequivocal route.

It has been shown, previously, that attempts to prepare 3-hydroxymethyl-6,8-dimethoxy-3,4-dihydro-1(2*H*)-naphthalenone from ethyl 5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (IIb), for example, through the lithium aluminum hydride reduction of the enol ether or ketal of IIb are not successful.1) The authors investigated to explore another method for blocking the keto group and reducing the ester group selectively on the lithium aluminum hydride reduction of IIb, and devised an excellent procedure applicable for the synthesis of α-sorigenin dimethyl ether. The method, essentially, consists of the lithium aluminum hydride reduction of ethyl 7,9-dimethoxy-4,5-dihydronaphth[2,1-*d*]isoxazole-4-carboxylate (IVb) and the successive alkaline treatment of the resulting 7,9-dimethoxy-4,5-dihydronaphth[2,1-*d*]isoxazole-4-methanol (VIb) to 1-oxo-3-hydroxymethyl-6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthonitrile (VIIb), which was led to α-sorigenin dimethyl ether by aromatization, methylation and hydrolysis.

In an initial study, the synthesis of 1-hydroxy-3-hydroxymethyl-2-naphthoic acid γ-lactone (IX) from ethyl 4-oxo-1,2,3,4-tetrahydro-2-naphthoate (IIa) was undertaken.

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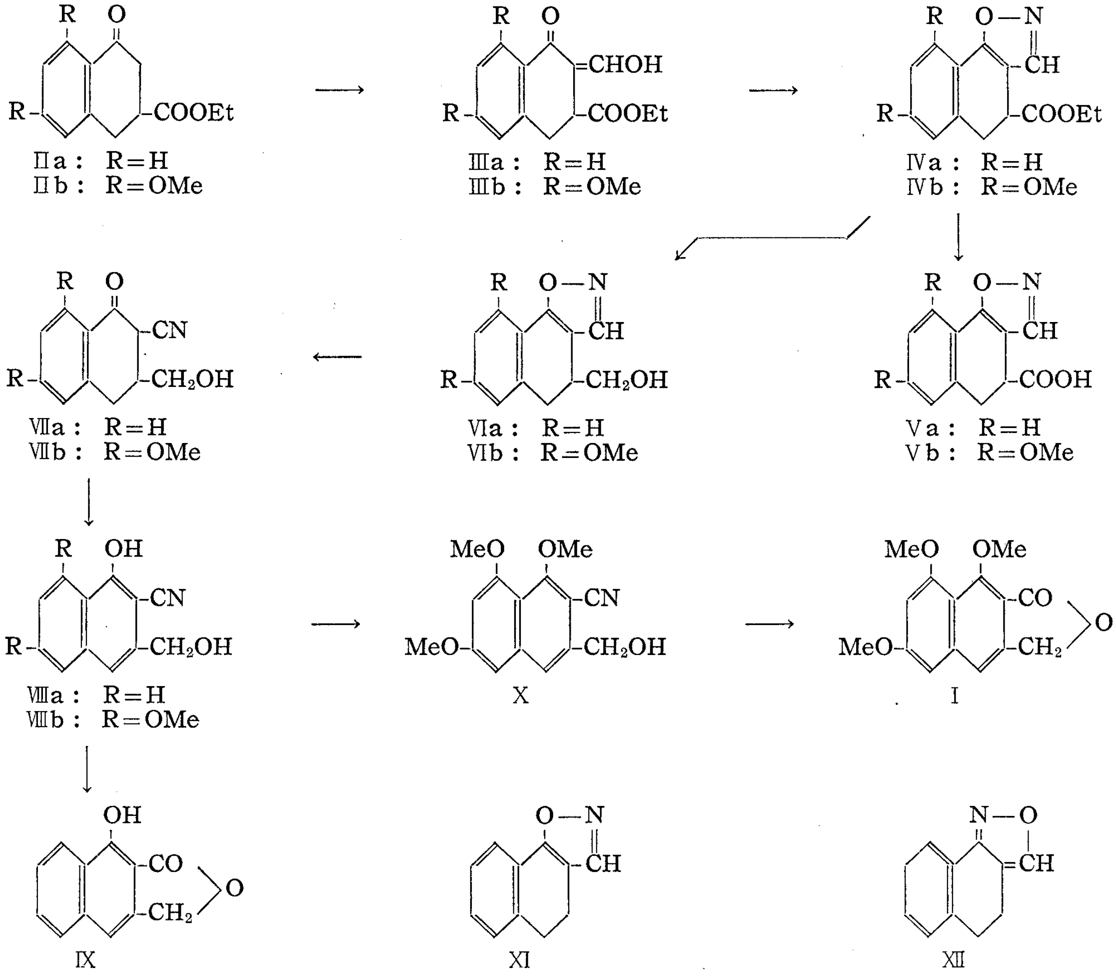
1) Part VI : This Bulletin, **11**, 312 (1963).

2) Part V : *Ibid.*, **11**, 309 (1963).

Formation of the isoxazole ring by the reaction of 2-hydroxymethylene-3,4-dihydro-1(2*H*)-naphthalenone and hydroxylamine hydrochloride was, first, reported by Auwers.[3] Afterwards, Johnson[4] investigated the reaction in detail. He found that the major product, 4,5-dihydronaphth[2,1-*d*]isoxazole (XI), was contaminated with a small amount of its isomer, 4,5-dihydronaphth[1,2-*c*]isoxazole (XII), and that, when the mixture of the above isomers was treated with sodium ethoxide, the major isomer XI was converted to alkaline soluble 1-oxo-1,2,3,4-tetrahydro-2-naphthonitrile whereas the minor isomer XII was unchanged and insoluble in alkaline aqueous solution. Concerning the reduction of the isoxazole derivative with lithium aluminum hydride, only a few reports[5] were found in literatures, in which the isoxazole ring, though in case of the reduction of the most stable type of the 3,5-disubstituted isoxazole, remained unchanged. Thus, if only the ester group in ethyl 4,5-dihydronaphth[2,1-*d*]isoxazole-4-carboxylate (IVa) were selectively reduced with lithium aluminum hydride to VIa, it would be expected to get IX by further reactions, that is, alkaline treatment, aromatization and hydrolysis.

Condensation of ethyl 3-hydroxymethylene-4-oxo-1,2,3,4-tetrahydro-2-naphthoate[6] (IIIa) with hydroxylamine hydrochloride in boiling acetic acid gave IVa, whose structure was supported by its hydrolysis with dil. hydrochloric acid to 4,5-dihydronaphth[2,1-*d*]-isoxazole-4-carboxylic acid (Va). Reduction of the ester IVa with lithium aluminum



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[3] K. v. Auwers, A. E. Nold: J. prakt. Chem., [2] **150**, 57 (1938).
[4] W. S. Johnson, W. E. Shelberg: J. Am. Chem. Soc., **67**, 1745 (1945).
[5] P. N. Craig, M. P. Olmstead: J. Org. Chem., **22**, 559 (1957); P. Grunanger: Gazz. chim. ital., **88**, 149 (1958).
[6] Part IV: This Bulletin, **11**, 306 (1963).

hydride in anhyd. ether at −60° gave 4,5-dihydronaphth[2,1-*d*]isoxazole-4-methanol (VIa), m.p. 89°, in 53% yield. A solution of sodium ethoxide in ethanol cleaved VIa at N-O bond to give 1-oxo-3-hydroxymethyl-1, 2, 3, 4-tetrahydro-2-naphthonitrile (VIIa), which was converted to IX[7] by bromination with bromine in chloroform, dehydrobromination with lithium chloride and dimethylformamide and hydrolysis with 10% potassium hydroxide solution.

The synthesis of α-sorigenin dimethyl ether was accomplished employing essentially the same sequence of reactions as those for IX. The isoxazole IVb, prepared from ethyl 3-hydroxymethylene-4-oxo-5, 7-dimethoxy-1, 2, 3, 4-tetrahydro-2-naphthoate[2], was reduced with lithium aluminum hydride in a mixture of anhyd. ether and anhyd. tetrahydrofuran at −60°, followed by treatment with a solution of sodium ethoxide in ethanol at room temperature to give the nitrile VIIb. Bromination and dehydrobromination converted VIIb to 1-hydroxy-3-hydroxymethyl-6, 8-dimethoxy-2-naphthonitrile (VIIIb), which was methylated to 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthonitrile (X) with methyl iodide and anhyd. potassium carbonate in acetone. Hydrolysis of X afforded 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone (I), m.p. 185°, which was identified with natural α-sorigenin dimethyl ether[8] and I prepared in the previous paper[1] by a mixed melting point determination and comparison of their infrared spectra.

Experimental

Ethyl 4,5-Dihydronaphth[2,1-*d*]isoxazole-4-carboxylate (IVa)——A mixture of 2.0 g. of ethyl 3-hydroxymethylene-4-oxo-1,2,3,4-tetrahydro-2-naphthoate,[6] 1.5 g. of $NH_2OH \cdot HCl$ and 20 cc. of AcOH was refluxed for 30 min. on an oil bath, and most of AcOH was removed under reduced pressure. The residue was dissolved in H_2O and extracted with Et_2O (20 cc. × 3). The Et_2O extract was washed successively with saturated $NaHCO_3$ solution and H_2O, dried over $MgSO_4$ and evaporated. Distillation of the residue gave 1.44 g. (73%) of IVa as a colorless oil, b.p.$_{0.07}$ 160~165° (bath temp.), m.p. 49° (from petr. ether). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1} : 1730 (CO_2Et), 1637 (C=N).

The above crude product (245 mg.) was refluxed with 4 cc. of dil. HCl (1:1) for 3 hr. After cooling, the solid was collected, washed with H_2O and dried. Colorless crystals (160 mg., 74%) were obtained, m.p. 170~172°. Recrystallization from EtOH gave colorless fine needles of 4,5-dihydronaphth[2,1-*d*]-isoxazole-4-carboxylic acid (Va), m.p. 172°. *Anal.* Calcd. for $C_{12}H_9O_3N$: C, 66.97; H, 4.22; N, 6.51. Found : C, 66.86; H, 3.98; N, 6.46. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1} : 1724 (CO_2H), 1634 (C=N).

4,5-Dihydronaphth[2,1-*d*]isoxazole-4-methanol (VIa)——A solution of 1.4 g. of IVa in 30 cc. of anhyd. Et_2O was added dropwise under vigorous stirring to a suspension of 1 g. of $LiAlH_4$ in 20 cc. of anhyd. Et_2O at −60° during a period of 30 min. After the addition was completed, stirring was continued at the same temperature for 3 hr. To the cooled reaction mixture (−60°) was added dropwise 10 cc. of AcOEt and then 50 cc. of dil. HCl, and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with AcOEt (50 cc. × 4). The organic layer and AcOEt extracts were combined, washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from 5 cc. of Et_2O to give colorless prisms, 610 mg. (53%), m.p. 87°. An analytical sample was prepared by several recrystallizations from Et_2O, m.p. 89°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found : C, 71.57; H, 5.54; N, 7.28. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1} : 3610, 3448 (OH), 1639 (C=N).

1-Oxo-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthonitrile (VIIa)——To a solution of 600 mg. of VIa in 20 cc. of anhyd. Et_2O was added a solution of EtONa in EtOH (prepared from 300 mg. of Na and 10 cc. of anhyd. EtOH) and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into a mixture of 50 cc. of Et_2O and 100 cc. of H_2O. The organic layer was extracted with 5% KOH (10 cc. × 3). The aqueous layer and alkaline washings were combined, acidified with dil. HCl (1:1) and extracted again with Et_2O (30 cc. × 3). The Et_2O extract was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent left a yellow solid, which was recrystallized from 2 cc. of benzene to give 568 mg. (96%) of fine prisms, m.p. 117~119°. An analytical sample was obtained

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7) Part I : This Bulletin, **10**, 887 (1963).

8) α-Sorigenin dimethyl ether was prepared by the methylation of α-sorigenin according to the method of Z. Nikuni (J. Agric. Chem. Soc. Japan, **14**, 352 (1938)).

by several recrystallizations from benzene, m.p. 120°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found : C, 71.73; H, 5.49; N, 7.14. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3484 (OH), 2247 (C≡N), 1686 (CO).

1-Hydroxy-3-hydroxymethyl-2-naphthoic Acid γ-Lactone (IX)——To a solution of 112 mg. of VIIa in 20 cc. of $CHCl_3$ was added dropwise a solution of 90 mg. of Br_2 in 10 cc. of $CHCl_3$ at room temperature over a period of 30 min. The mixture was stirred for 30 min., washed with saturated $NaHCO_3$ solution and then H_2O, dried over $MgSO_4$ and evaporated. To the residual oil was added 200 mg. of LiCl and 5 cc. of dimethylformamide, and the mixture was heated on a boiling water bath for 3 hr. After cool, the solution was diluted with 10 cc. of H_2O and extracted with AcOEt (10 cc. × 3). The AcOEt extract was washed with $NaHCO_3$ solution and H_2O, dried over $MgSO_4$, and evaporated to give 85 mg. of a solid. This crude solid (50 mg.) was refluxed with 5 cc. of 10% KOH for 3 hr. The mixture was acidified with dil. HCl and warmed on a water bath for 10 min. After cooling, the precipitate was collected, washed with H_2O and recrystallized from EtOH to give 20 mg. (overall yield from VIIa; 30%) of colorless needles, m.p. 226°, which was identified with an authentic sample of IX obtained in the previous paper[7] by a mixed melting point determination and comparison of their IR spectra. *Anal.* Calcd. for $C_{12}H_8O_3$: C, 71.99; H, 4.03. Found : C, 72.33; H, 4.01. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3388 (OH), 1724 (CO).

Ethyl 7,9-dimethoxy-4,5-dihydronaphth[2,1-*d*]isoxazole-4-carboxylate (IVb)——A mixture of 405 mg. of ethyl 3-hydroxymethylene-4-oxo-5,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate,[2] 400 mg. of $NH_2OH \cdot HCl$ and 10 cc. of AcOH was refluxed on an oil bath for 30 min. The reaction mixture was treated in a similar manner to that described for the preparation of IVa to give 234 mg. (58%) of IVb as a light red oil, $\text{b.p}_{0.08}$ 200° (bath temp.). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1733 (CO_2Et), 1631 (C=N).

The crude ester IVb (200 mg.) was hydrolyzed with 10% H_2SO_4 (4 cc.) to give 145 mg. (98%) of 7,9-dimethoxy-4,5-dihydronaphth[2,1-*d*]isoxazole-4-carboxylic acid (Vb) as light purple needles of m.p. 180°, after one recrystallization from 1 cc. of EtOH. An analytical sample was obtained as colorless fine needles by several recrystallizations from EtOH, m.p. 182°. *Anal.* Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found : C, 61.04; H, 4.76; N, 5.18.

1-Oxo-3-hydroxymethyl-6,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthonitrile (VIIb)——A solution of 4.5 g. of IVb in 50 cc. of anhyd. tetrahydrofuran was added dropwise, with vigorous stirring, to a suspension of 5 g. of $LiAlH_4$ in 200 cc. of anhyd. Et_2O at −60° over a period of 2 hr. The mixture was stirred for 4.5 hr. at the same temperature and then treated by the same procedure as that for the preparation of VIa. The resulting red oily product was purified by chromatography using silica gel and $CHCl_3$ as a eluent. The first brownish band eluted gave a small amount of unchanged starting ester IVb, and the second pale yellow band eluted gave 3.15 g. (81%) of VIb as a light orange viscous oil. To an ice-cooled solution of 3.1 g. of the crude VIb in 20 cc. of anhyd. EtOH was added an EtOH solution of EtONa (prepared from 0.5 g. of Na and 10 cc. of anhyd. EtOH) and the mixture was stirred at room temperature for 1 hr., and treated in a like manner as that for the preparation of VIIa. The AcOEt extract gave 1.42 g. (45%) of colorless crystals, m.p. 158~160°, which was recrystallized from Me_2CO to give colorless fine prisms, m.p. 164°. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found : C, 64.59; H, 6.01; N, 5.49. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3468 (OH), 2252 (C≡N), 1667 (CO).

1-Hydroxy-3-hydroxymethyl-6,8-dimethoxy-2-naphthonitrile (VIIIb)——To a solution of 406 mg. of VIIb in 40 cc. of AcOH was added dropwise a soluton of 246 mg. of Br_2 in 40 cc. of AcOH at room temperature over a period of 30 min. The reaction mixture was stirred for further 30 min., and poured into 500 cc. of H_2O. The resulting acidic solution was neutralized with 120 g. of $NaHCO_3$, the precipitate was collected, washed with H_2O and dried, giving 404 mg. (76%) of a colorless bromide, m.p. 199° (decomp.). The crude bromide (180 mg.) was dissolved in anhyd. morpholine (15 g.) and allowed to stand at room temperature for 2 days. The reaction mixture was poured into ice-dil. HCl and extracted with AcOEt (100 cc. × 3). The AcOEt extract was washed with H_2O, dried over $MgSO_4$ and evaporated. The residue was recrystallized from EtOH to give 101 mg. (74%) of colorless needles, m.p. 221° An analytical sample was prepared by recrystallizations form EtOH, m.p. 224°. *Anal.* Calcd. for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05; N, 5.40. Found : C, 64.71; H, 4.81; N, 5.34.

3-Hydroxymethyl-1,6,8-trimethoxy-2-naphthonitrile (X)——A mixture of 95 mg. of VIIIb, 2 cc. of MeI, 10 cc. of anhyd. Me_2CO and 100 mg. of anhyd. K_2CO_3 was heated under reflux on a boiling water bath for 12 hr. and the solvent was removed. Water was added to the residue, the insoluble material collected, washed with H_2O, dried and recrystallized from EtOH giving 80 mg. (80%) of colorless needles, m.p. 202°. *Anal.* Calcd. for $C_{15}H_{15}O_4N$: C, 65.29; H, 5.53; N, 5.13. Found : C, 65.52; H, 5.60; N, 5.00.

3-Hydroxymethyl-1,6,8-trimethoxy-2-naphthoic Acid γ-Lactone (α-Sorigenin Dimethyl Ether) (I)——A solution of 37 mg. of X, 340 mg. of KOH, 2 cc. of H_2O and 5 cc. of EtOH was refluxed for 10 hr. Most of EtOH was removed by distillation, the residual alkaline solution was acidified with dil. HCl (1:1) and warmed on a water bath for a few min. After cooling, the resulting precipitate was dissolved in AcOEt. The AcOEt solution was washed with H_2O, dried over $MgSO_4$, and the solvent was removed to give 29 mg. of a solid. Recrystallization from EtOH gove 20 mg. (69%) of colorless needles, m.p.

182°, which was raised up to 185° by further recrystallizations. This compound was to be identical with natural α-sorigenin dimethyl ether (m.p. 185°)[8] and the previously reported γ-lactone I (m.p. 185°)[1] by a mixed melting point determination and comparison of their IR spectra. *Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.63; H, 5.34. IR $\nu_{max}^{CHCl_3}$ 1754 (CO) cm^{-1}.

Summary

The synthesis of α-sorigenin dimethyl ether, 3-hydroxymethyl-1,6,8-trimethoxy-2-naphthoic acid γ-lactone (I), by an unequivocal route as shown in chart is described. The reactions employed for preparing the 1-oxo-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthonitrile (VII) from the ethyl 1-oxo-1,2,3,4-tetrahydro-2-naphthoate II via the intermediates, III, IV, and VI, would provide a new method for protecting the keto-group towards lithium aluminum hydride reduction.

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55. Masuo Akagi, Yoneshiro Oketani, Masahiko Takada, and Tetsuya Suga: Studies on Metabolism of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone. II.[*1] Physiological Disposition and Metabolic Fate of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone.

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In the previous paper[*1] the estimation of hypnotic, 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (MTQ) in biological materials have been reported, and in view of clinical and toxicological importance, a study was made of the physiological disposition and metabolic fate of MTQ.

Experimental and Results

Animals, Diet and Dosage——The rabbits (2.8～3.0 kg., body wt.) were kept on 50 g. of oats and 300 g. of cabbage. MTQ was administered orally in gelatin capsules in a dose of 200 mg./kg. body weight.

Wistar rats (180～200 g., body wt.) were maintained on solid food[*4] and water throughout the the experiments. MTQ (200 mg. or 100 mg./kg. body wt.) was administered by stomach tube as a 2% (w/v) suspension in 5% (w/v) aqueous gum arabic solution. Rabbits and rats were housed in metabolism cages, and urinary collection was made every 24 hr. after administration of the drug.

Estimation of MTQ in Biological Materials——The rats each received MTQ were decapitated and their blood and organs were rapidly removed. The drug in urine, plasma and tissues was measured by a spectrophotometric method described by Akagi *et al.*[*1]

Physiological Disposition of MTQ

Plasma Levels of MTQ after Oral Administration to Human Subjects[*5]——Two human subjects

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[*1] Part I. M. Akagi, Y. Oketani, M. Takada: This Bulletin, **11**, 62 (1963).

[*2] Nishi-5-chome, Kita-12-jo, Sapporo (赤木満洲雄, 桶谷米四郎, 須賀哲彌).

[*3] *Ibid.* (高田昌彦).

[*4] Oriental Yeast & Co. Ltd., Tokyo.

[*5] The authors are indebted to Prof. N. Suwa of the University of Hokkaido for providing the human blood samples used in this study.