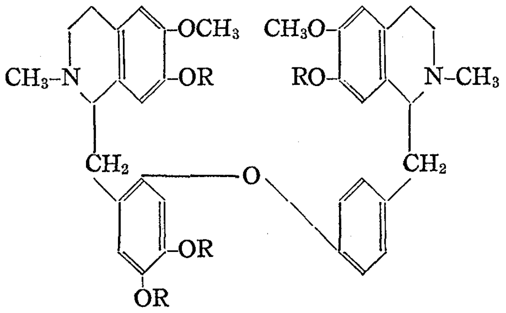
Chem. Pharm. Bull. 14(1) 78~82 (1966)

UDC 547.94.07 : 547.833.07

14. Tetsuji Kametani and Haruhiko Yagi : Bisbenzylisoquinoline Alkaloids and Related Compounds. VII.[*1] A Total Synthesis of the Stereoisomeric Mixture of Magnolamine.[*2,*3]

(*Pharmaceutical Institute, Tohoku University School of Medicine*[*4])

Magnolamine, $C_{36}H_{40}O_7N_2$, m.p. 119°, one of the alkaloids of Magnoliaceae plants, was isolated from the leaves of *Magnolia fuscata* belonging to the order of Caucasian Magnoliaceae by Proskurnina and Orekhoff[1] in 1939. The structure of magnolamine was assigned as I by chemical methods.[2~4] However, a total synthesis of magnolamine has not yet been achieved.



I : R=H
II : R=$CH_2C_6H_5$

The purpose of the present investigation was to study the cyclization of the diamide (IX) in order to obtain the corresponding dihydroisoquinoline derivative (X) and its dimethiodide (XI) as possible intermediates for the synthesis of magnolamine (I). A study of the reduction of XI, followed by hydrolysis of O-tetrabenzylmagnolamine (II), eventually led to a synthesis of racemic magnolamine that supports the structure (I).

Ullmann reaction of methyl 2-bromo-4,5-methylenedioxybenzoate (III)[5] with methyl 4-hydroxybenzoate gave dimethyl 2,4′-oxy-4,5-methylenedioxydibenzoate (IV) as colorless prisms. Cleavage of the methylenedioxy radical of the biphenyl ether (IV) by the action of phosphorus pentachloride followed by hydrolysis[6] was carried out to give the corresponding 4,5-dihydroxy-derivative (V), whose methylation with diazomethane afforded methyl magnolamate[7] (Va), m.p. 132.5~133°. Benzylation of the above compound (V) in the presence of sodium hydroxide in methanol afforded dimethyl 2,4′-oxy-4,5-bisbenzyloxydibenzoate (VI), which was converted into the corresponding dicarboxylic acid (VII) by hydrolysis. Recrystallization of this acid from dimethyl sulfoxide and water yielded 2,4′-oxy-4,5-bisbenzyloxydibenzoic acid (VII) as colorless feathers, m.p. 256~257°, which was converted into the acid chloride (VIII) by chlorination with thionyl chloride.

Arndt-Eistert reaction[8] of 3-methoxy-4-benzyloxyphenethylamine with the diazoketone which was obtained from the acid chloride (VIII) gave the diamide (IX). Bischler-

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[*1] Part VI. T. Kametani, S. Takano, Y. Yanase, C. Kibayashi, H. Iida, S. Kano, and K. Sakurai : This Bulletin, **14**, 73 (1966).

[*2] This forms Part CXXXIV of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.

[*3] Short communication was reported in Tetrahedron Letters, No. 15, 953 (1965).

[*4] Kita-4-bancho, Sendai (亀谷哲治, 八木治彦).

1) N.F. Proskurnina, A.P. Orekhoff : J. Gen. Chem. U.R.S.S., **9** (71), 126 (1939); Chem. Zentr., **110** I, 423 (1939).

2) *Idem* : *Ibid.*, **16**, 129 (1946); Chem. Abstr., **41**, 460 (1947).

3) M. Tomita, E. Fujita : Yakugaku Zasshi, **70**, 411 (1950).

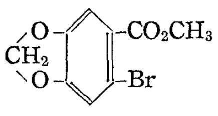
4) M. Tomita, E. Fujita, T. Nakamura : *Ibid.*, **71**, 1075 (1951); Chem. Abstr., **46**, 5060 (1952).

5) E. Oertly, A. Pictet : Ber., **43**, 1339 (1910); W. Baker : J. Chem. Soc., **1926**, 1075.

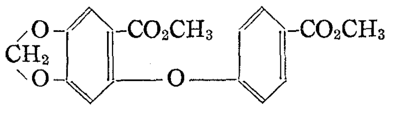
6) J.S. Buck, F.J. Zimmermann : Org. Syntheses, Coll. Voll. **II**, 549.

7) M. Tomita : This Bulletin, **4**, 411 (1956).

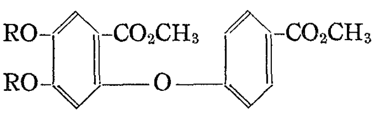
8) M.S. Newman, R.F. Beal : J. Am. Chem. Soc., **72**, 5163 (1950).



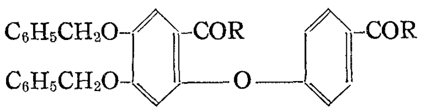
III



IV

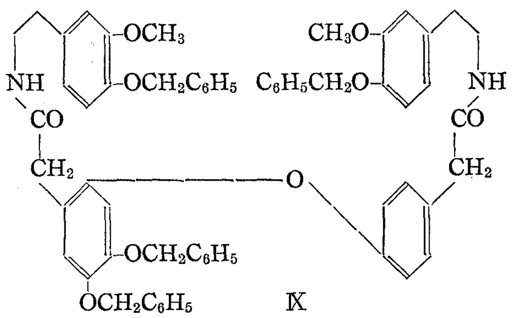


V : R=H
Va : R=CH_3

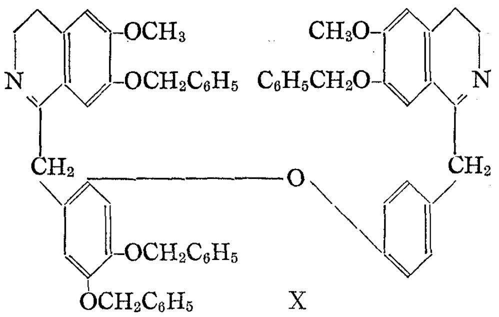


VI : R=OCH_3
VII : R=OH
VIII : R=Cl

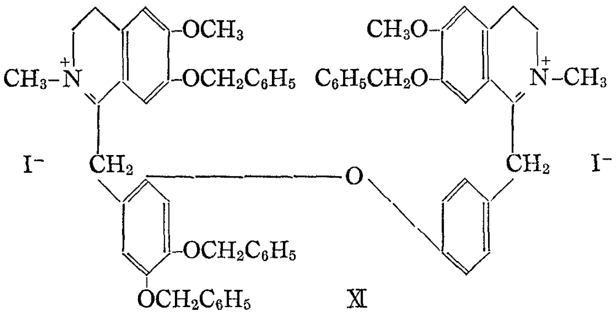
Napieralski cyclization of the above diamide (IX) with phosphoryl chloride in benzene afforded the dihydroisoquinoline derivative (X) as a yellowish-brown glass. Reduction of the amorphous dimethiodide (XI), which could not be purified by recrystallization, with sodium borohydride in methanol or chloroform-methanol afforded a crude O-tetrabenzylmagnolamine (II). In this case the attempts to separate one of the two diastereoisomers in a crystalline state under a variety of procedure, for instance, alumina-, paper-, cellulose-, and thin-layer-chromatography, and preparative gas chromatography, were examined, but resulted in failure.



IX



X



XI

Hydrolysis of the above O-tetrabenzylmagnolamine (II) with ethanolic concentrated hydrochloric acid gave a stereoisomeric mixture of magnolamine as a yellow syrup which formed a pale yellowish-brown powder on being triturated with hexane.

The synthetic magnolamine and natural one behaved similarly on paper-chromatography. The infrared (in chloroform) and ultraviolet (in ethanol) spectra were superimposable on those of natural magnolamine donated by Prof. M. Tomita, but attempted purification in a crystalline state at this stage failed. Therefore, it is not obvious whether our synthetic magnolamine would be the mixture of racemic magnolamine and its diastereoisomer or not, but it was proved that our synthetic sample had the same planar structure (I) as the natural magnolamine. These facts reveal that the total synthesis of the stereoisomeric mixture of magnolamine has been accomplished.

To our regret, comparison of nuclear magnetic resonance spectra of synthetic sample with one of natural magnolamine could not be done because the amount of natural product was not so enough for measurement. Our synthetic sample showed phenolic OH at 5.41~5.70 τ (4H), methoxyl CH_3 at 6.21 τ (broad singlet) (6H) and N-CH_3 at 7.60 τ (broad) (6H). Replacement of synthetic magnolamine with deuterium oxide removed the signal of OH group at 5.41~5.70 τ.

Experimental

IR and UV spectra were measured on a Type EPI-2 Hitachi infrared spectrophotometer and Type EPI-3 Hitachi recording spectrophotometer, respectively. Nuclear magnetic resonance spectrum was determined on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference. Melting points were determined on a Kofler block and uncorrected.

Dimethyl 2,4′-Oxy-4,5-methylenedioxydibenzoate (IV)——A mixture of methyl 4-hydroxybenzoate (31.6 g.), methyl 2-bromo-4,5-methylenedioxybenzoate[5] (Ⅲ) (50 g.), potassium carbonate (25.9 g.), copper powder (11.4 g.), and pyridine (1 ml.) was uniformly admixed, heated at 120°(bath) (a gas began to evolve) and then at 135~140° for 6 hr. The mixture was then cooled and extracted with hot chloroform, from which copper powder was removed by filtration. The dark reddish-purple solvent was washed with 10% sodium hydroxide, water, 10% hydrochloric acid, and water and then dried (Na_2SO_4). Removal of the solvent gave a pale brown solid (57.6 g.), which was chromatographed on alumina. Evaporation of the first chloroform eluate afforded dimethyl 2,4′-oxy-4,5-methylenedioxydibenzoate (Ⅳ) (40 g., 65.6%) as colorless prisms, m.p. 94~96°, which was recrystallized from methanol to give colorless prisms, m.p. 96~97°. *Anal.* Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27. Found : C, 61.93; H, 3.90. IR ν_{max}^{KBr} cm^{-1} : 1718, 1710 (ester C=O).

Dimethyl 2,4′-Oxy-4,5-dihydroxydibenzoate (V)——A mixture of the preceding ester (Ⅳ) (33.8 g.) and phosphorus pentachloride (42.6 g.) was gradually heated at 120~130° in an oil-bath, giving a red clear solution (a vigorous gas evolution of hydrochloride was observed). After 2 hours' refluxing, the mixture was distilled *in vacuo* to give a reddish viscous syrup, to which water (100 ml.) was added and the mixture was heated under reflux at 110° in an oil-bath for 1 hr. After a vigorous gas evolution had been observed, a reddish syrup solidified and collected by filtration. Recrystallization from methanol-water afforded the 4,5-dihydroxy-derivative (V) (30.6 g., 93.9%) as colorless needles, m.p. 148~149°. *Anal.* Calcd. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43. Found : C, 60.36; H, 4.43. IR ν_{max}^{KBr} cm^{-1} : 3413, 3279 (OH), 1692 (C=O).

A solution of V (0.5 g.) in methanol (20 ml.) was added to an excess of diazomethane in ether. After the mixture was allowed to stand in a refrigerator for 2 days, removal of the solvent and recrystallization from methanol gave methyl magnolamate (Va) (0.5 g.) as colorless needles, m.p. 132.5~133° (lit.[4,7] m.p. 132.5~133°).

Dimethyl 2,4′-Oxy-4,5-bisbenzyloxydibenzoate (VI)——a) To a solution of the preceding ester (V) (10 g.) in N,N-dimethylformamide (30 ml.) were added potassium carbonate (4.34 g.) and benzyl chloride (9.6 g.), and the mixture was heated under reflux at 140~150° in an oil-bath for 15 hr. The reddish-brown mixture was poured into water (250 ml.), and extracted with benzene. The benzene layer was washed with 10% sodium hydroxide, water, 10% hydrochloric acid and water. Removal of the dried (Na_2SO_4) solvent gave a red viscous syrup, which solidified on being triturated with a small amount of methanol and collected by filtration, to give the bisbenzyloxy-derivative (Ⅵ) (4.2 g., 26.7%) as colorless needles, m.p. 90~95°. Recrystallization from methanol afforded colorless needles, 95~96°. *Anal.* Calcd. for $C_{30}H_{26}O_7$: C, 72.28; H, 5.26. Found : C, 72.38; H, 5.10. IR ν_{max}^{KBr} cm^{-1} : 1724, 1712 (ester C=O).

b) A mixture of V (5 g.), potassium carbonate (2.17 g.), and benzyl chloride (5 g.) in dioxane (50 ml.) was heated under reflux at 110° in an oil-bath for 10 hr. Similar treatment of the reaction mixture as above [method (a)] gave the bisbenzyloxy-derivative (Ⅵ) (2.7 g., 35%).

c) The preceding ester (V) (5.4 g.) was added to a methanol solution of sodium methoxide which was prepared from metallic sodium (0.5 g.) and dry methanol (40 ml.), and the mixture was refluxed for 8 hr. After the reaction, the solvent was removed by distillation under reduced pressure, to give a brown syrup, from which the compound (Ⅵ) (1 g., 11.5%) was obtained by the same treatment as above.

d) A mixture of V (3 g.), sodium hydroxide (0.8 g.), benzyl chloride (3.6 g.), and methanol (40 ml.) was refluxed on a water-bath for 8 hr. After removal of the solvent, the residue was admixed with water and treated as above, to give the compound (Ⅵ) (3.2 g., 68.1%).

2,4′-Oxy-4,5-bisbenzyloxydibenzoic Acid (VII)——A mixture of the preceding bisbenzyloxy-derivative (Ⅵ) (6.5 g.), potassium hydroxide (3 g.), water (2 ml.), and ethanol (58 ml.) was refluxed on a water-bath for 3 hr., and the solvent was distilled off, to give a colorless solid, to which water (100 ml.) was added for dissolving it. The resultant alkaline solution was acidified with 10% hydrochloric acid and a colorless gel-like precipitate was collected on a filter by filtration. This was washed with water and dried, to give the acid (VII) (5.5 g., 90%) as a colorless powder, m.p. 251~255°. Recrystallization from dimethyl sulfoxide-water afforded colorless feathers, m.p. 256~257°. *Anal.* Calcd. for $C_{28}H_{22}O_7$: C, 71.48; H, 4.71. Found : C, 71.33; H, 4.73. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 2674~2222 (OH), 1701, 1686 (C=O).

4,5-Bisbenzyloxy-2,4′-bis(3-methoxy-4-benzyloxyphenethylaminocarbonylmethyl)biphenyl Ether (IX). a) **The Formation of Diazoketone**——The acid chloride (VIII) was prepared by refluxing mildly the above acid (VII) (2 g.) with thionyl chloride (15 ml.) in the presence of dried pyridine (1 drop) on a water-bath for 1 hr. and then removing the large excess of thionyl chloride. The chloride was thus obtained as colorless crystals (2.1 g.), m.p. 117~119°. A solution of the above acid chloride (VIII) in dry ether (500 ml.) was added to a solution of diazomethane in dry ether (220 ml.), which was prepared from *p*-toluenesulfonylmethylnitrosoamide (25 g.), potassium hydroxide (7 g.), and ethanol (50 ml.). After being allowed to stand at room temperature in a refrigerator overnight, the yellowish resultant solution was concentrated and cooled to give the crystalline diazoketone (3.1 g.) as pale yellow needles, m.p. 109~112°.

b) **The Formation of the Diamide** (IX)——A solution of silver benzoate[8] (2.2 g.), prepared from silver nitrate and sodium benzoate according to Newman's procedure, in triethylamine (22 ml.) was filtered to remove a small amount of precipitates. Soon after the addition of a few drops of this solution to a mixture of the above diazoketone (3.1 g.) in dry benzene (180 ml.) and 3-methoxy-4-benzyloxyphenethylamine (3.5 g.) at room temperature, the reaction mixture turned reddish-purple and evolution of nitrogen commenced. As soon as the evolution of nitrogen slacked a new addition of silver benzoate solution was made. After a total silver benzoate solution had been added, the mixture was allowed to stand at room temperature for 1 hr. and then heated to reflux on a water-bath for 2 hr.

The cooled reaction mixture was filtered, washed with 3% sulfuric acid, 5% sodium hydrogen carbonate, 10% sodium hydroxide, and water, and dried (Na_2SO_4). Removal of the solvent afforded the diamide (IX) as a reddish viscous oil (4.0 g., 96.4%), which was recrystallized from benzene to give a colorless powder, m.p. 167~168°. *Anal.* Calcd. for $C_{62}H_{60}O_9N_2$: C, 76.21; H, 6.19; N, 2.87. Found : C, 76.03; H, 5.96; N, 3.15. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 3305 (NH), 1642 (amide, C=O), 746 and 696.9 (monosubstituted benzene).

4,5-Bisbenzyloxy-2,4′-bis(6-methoxy-7-benzyloxy-3,4-dihydro-1-isoquinolylmethyl)biphenyl Ether (X)——A mixture of the above diamide (IX) (3 g.) dry benzene (50 ml.), and phosphoryl chloride (7 ml.) was refluxed at 85~90° on a water-bath for 5 hr. in a current of nitrogen, giving a reddish-brown solution. An excess of ligroin (400 ml.) was added to the cooled reaction mixture and allowed to stand overnight. An upper layer was removed by decantation, and the residue was repeatedly washed with ligroin. The resultant brown residue was extracted with chloroform (100 ml.). The solvent was washed with 10% sodium hydroxide and water and dried (K_2CO_3). Evaporation of the solvent in a current of nitrogen afforded the dihydroisoquinoline derivative (X) (2.2 g.) as a pale brown viscous syrup, which became a caramel-like substance being allowed to stand, but could not be crystalline. Recrystallization of the dipicrate from chloroform-ether gave a yellowish-orange powder, m.p. 103~105° (decomp.). *Anal.* Calcd. for $C_{62}H_{56}O_7N_2 \cdot 2C_6H_3O_7N_3$: N, 8.00. Found : N, 7.54. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1631 (shoulder), 1613 (C=N), 740.7 and 696.9 (monosubstituted benzene).

4,5-Bisbenzyloxy-2,4′-bis(6-methoxy-7-benzyloxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)biphenyl Ether (O-Tetrabenzylmagnolamine) (II)——A mixture of the above dihydroisoquinoline (X) (0.9 g.) and methyl iodide (10 ml.) was allowed to stand for 2 days at room temperature in the presence of nitrogen. An excess of ether was added to the reaction mixture and the precipitate was collected to give the dimethiodide (XI) as a pale brown powder (1.1 g.), m.p. 181° (decomp.) (sinters at 165~180°), which was too easy to become resinous while recrystallization, and, therefore, used without purification in the following reaction.

To a solution of above dimethiodide (XI) (1.8 g.) in a mixture of chloroform (18 ml.) and ethanol (30 ml.) was added in small portions with shaking sodium borohydride (2 g.) within 1 hr., and the mixture was allowed to stand at room temperature for 0.5 hr. The solvent was distilled off, the residue treated with water (100 ml.) and extracted with benzene. The benzene extract was washed with 10% sodium hydroxide and water, dried (K_2CO_3), and evaporated, leaving the O-tetrabenzylmagnolamine (II) as a reddish pink viscous syrup (1.7 g.). This was chromatographed on alumina (50 g.), giving a pale red benzene-chloroform (1:1) eluate. Evaporation of the eluate gave a reddish glass (0.8 g.), whose diperchlorate was recrystallized from chloroform-ether to give a colorless powder, m.p. 115~118°. *Anal.* Calcd. for $C_{64}H_{66}O_{15}N_2Cl$: C, 65.47; H, 5.67; N, 2.39. Found : C, 65.69; H, 5.77; N, 2.44.

Stereoisomeric Mixture of Magnolamine (I)——A solution of the above O-tetrabenzylmagnolamine (II) (0.5 g.), ethanol (20 ml.) and concentrated hydrochloric acid (20 ml.) was refluxed on a water-bath for 5 hr. in a current of nitrogen. After the ethanol was removed off *in vacuo*, the resultant glassy substance was basified with 28% ammonium hydroxide (15 ml.) and extracted with ethyl acetate (500 ml.) repeatedly. The extract was washed with sodium chloride solution and dried (Na_2SO_4). Removal of the solvent gave a reddish glass. Recrystallization from chloroform petroleum ether gave 4,5-dihydroxy-2,4′-bis (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl) biphenyl ether (I) as a pale brown powder (16 mg.), m.p. 112~116° (sinters at 102°). *Anal.* Calcd. for $C_{36}H_{40}O_7N_2$: C, 70.57; H, 6.58; N, 4.57. Found : C, 70.64; H, 6.67; N, 4.65. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3610 (OH) and 2817 (N-CH_3). UV λ_{max}^{EtOH} mμ (log ε) : 286 (4.07).[*5] Rf (paper chromatography) (synthetic) 0.497, (natural) 0.489 [BuOH-AcOH-H_2O (5:1:4) as solvent; the spots were detected by their fluorescence under UV light (short wave 2536 Å, cycle 50)]. NMR (τ) spectrum ($CDCl_3$ as solvent and tetramethylsilane as internal reference were used) showed 5.41~5.70 (OH) (4H), 6.21 (broad singlet) (6H) (OCH_3) and 7.60 (broad doublet) (6H) (NCH_3).

We thank Prof. M. Tomita of Kyoto University for a gift of natural magnolamine, Miss F. Seto and N. Nanjo for microanalyses, and Miss T. Oikawa for infrared spectra.

Summary

The diamide (Ⅸ) was prepared from the 2,4′-oxy-4,5-bisbenzyloxydibenzoic acid (Ⅷ) and 3-methoxy-4-benzyloxyphenethylamine by Arndt-Eistert reaction. Cyclization of Ⅸ gave the dihydroisoquinoline (Ⅹ); reduction of the dimethiodide (Ⅺ) with sodium borohydride, followed by hydrolysis with concentrated hydrochloric acid-ethanol (1:1), gave the stereoisomeric mixture of magnolamine (I).

(Received June 30, 1965)

[*5] Natural magnolamine, UV λ_{max}^{EtOH} mμ (log ε) : 286 (4.09).

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UDC 547.458.2.07

15. Shigeru Takanashi, Yoshinobu Hirasaka, Minoru Kawada, and Morizo Ishidate[*2] : Synthesis of Amino Sugar Containing Disaccharides. The Synthesis of Hyalobiuronic Acid and Chondrosine.[*3]

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and Tokyo Biochemical Research Institute[*2])

Biochemical interests have been taken in aminosugar containing polysaccharides. Hyaluronic acid and chondroitin sulfuric acid A or C are typical of these polysaccharides. The former is composed of equivalent quantities of D-glucuronic acid and N-acetyl-D-glucosamine, and the latter consists of D-glucuronic acid and sulfonated N-acetyl-D-galactosamine. The unit disaccharide of hyaluronic acid is hyalobiuronic acid and that of chondroitin sulfuric abid A or C is chondrosine.

In a preliminary communication, there has been outlined the synthesis of these disaccharides.[1)]

Hyalobiuronic acid was isolated form hydrolysate of human umbilical cord hyaluronate[2)] and its structure was shown to be 2-amino-2-deoxy-3-O-β-D-glucopyranuronosyl-D-glucose by Weissmann, *et al.*[3)] Chondrosine was obtained in crystalline form[4)] by Davidson *et al.*[5)] and characterized as 2-amino-2-deoxy-3-O-β-D-glucopyranuro-

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[*2] *Ibid.* (石館守三).

[*3] Part of this work was presented at the 35th Annual Meeting of the Japanese Biochemical Sociey, Tokyo, 1962.

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5) *Idem* : *Ibid.*, **77**, 4796 (1954).