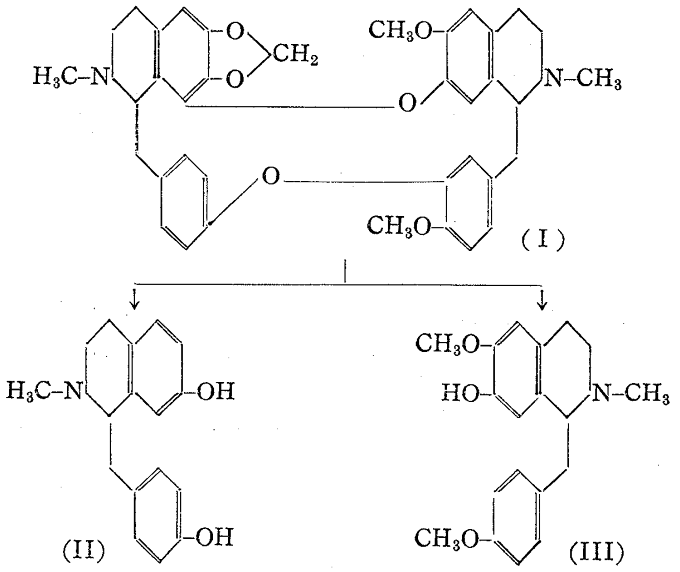
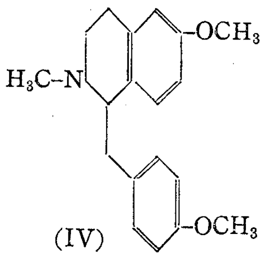
48. **Yoshio Sasaki**: Studies on the Alkaloids of Menispermaceous Plants. CXXVI.[1] Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia. (5). Structure of the Bisected Phenolic Base. (2)*

*(Pharmaceutical Institute, Medical Faculty, University of Kyoto**)*

In an earlier investigation[1] on the structure of A-base, m.p. 205~207°(decomp.), one of the bisected phenolic bases obtained by the fission of cepharanthine (I) by means of sodium in liquid ammonia, it was reported that the O,O-dimethyl ether methyl-methine of A-base was not identical with any of the two methyl-methines derived from *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IV) but with the O-methyl ether methyl-methine of the phenolic base obtained by an analogous mode of fission of *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (V). As a result, it was suggested that the above bisected phenolic base, m.p. 205~207°(decomp.) (A-base), should be *d*-1-(4′-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II).

In the present series, further investigation has been carried out to furnish a positive evidence for this assumption.





The catalytic hydrogenation of the O,O-dimethyl ether methyl-methine (VII) derived from the bisected phenolic base, m.p. 205~207°(decomp.) (A-base), yielded the hydromethine (VIII), the methiodide of which, on degradation by the Hofmann procedure, was led to the des-N base (IX). This, on oxidation with potassium permanganate, was converted into its corresponding carboxylic acid (X), which was then decarboxylated to afford a substance, m.p. 36~38°. If the bisected phenolic base obtained by the fission of cepharanthine is *d*-1-(4′-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II), the substance, m.p. 36~38°, here obtained must correspond to 3,4′-dimethoxy-α,β-diphenylethane (XI) considering its reaction process. Consequently, in order to make a direct comparison, it was decided to synthesize the substance corresponding to (XI). 3,4′-Dimethoxy-α,β-diphenylethane (XI) was the one that Asahina and Asano[2] had previously

---

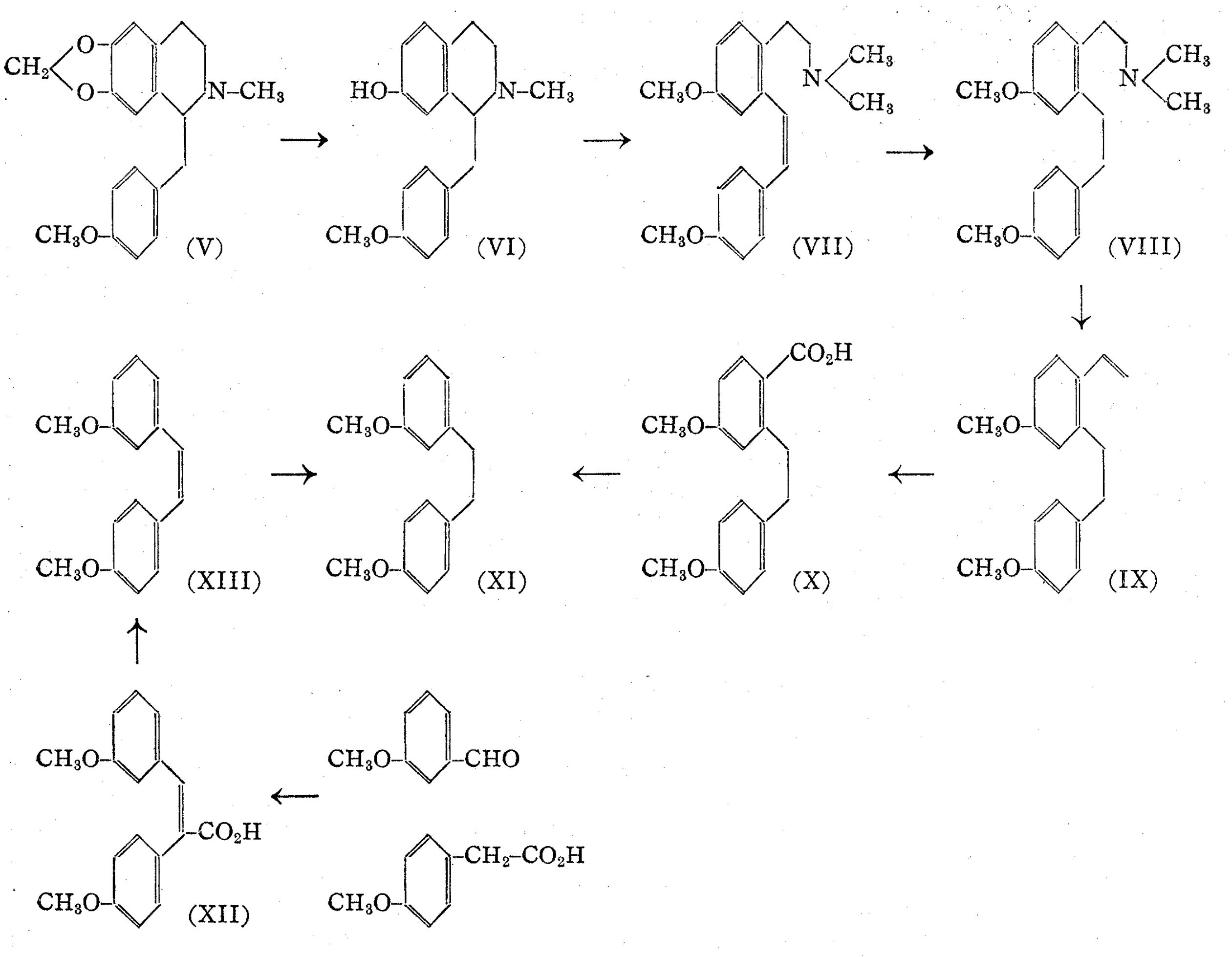
* This paper constitutes a part of a seriees entitled "Studies on the Alkaloids of Menispermaceous Plants" by Masao Tomita.

** Yoshida-konoe-cho, Sakyo-ku, Kyoto (佐々木喜男).

1) Part CXXV. Part (4). Y. Sasaki, H. Ohnishi, N. Satoh: This Bulletin, **3**, 178(1955).

2) Y. Asahina, J. Asano: Ber., **63**, 429(1930).

obtained as a degradation product of hydrangeaic acid. At that time, however, it was not induced to crystallize but was characterized by its derivatives, 3,4'-dihydroxy-α,β-diphenylethane and 3,4-dibenzoyloxy-α,β-diphenylethane. The present author attempted to synthesize it by a route quite different from that employed by them. The reaction of 3-methoxybenzaldehyde with 4-methoxyphenylacetic acid yielded 3,4'-dimethoxystilbene-β-carboxylic acid (XII), which on decarboxylation, gave rise to 3,4'-dimethoxystilbene (XIII). Subsequently, its catalytic reduction resulted in producing 3,4'-dimethoxy-α,β-diphenylethane (XI). This substance formed colorless needles, m.p. 36~38°, the identity of which was confirmed by admixture with the substance of m.p. 36~38°, derived from the bisected phenolic base (A-base) by the fission of cepharanthine.



From the foregoing experimental results, it follows that the bisected phenolic base, m.p. 205~207° (decomp.) (A-base) and its O,O-dimethyl ether, m.p. 115~116°, are respectively, *d*-1-(4'-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II) and *d*-1-(4'-methoxybenzyl)-7-methoxy-N-methyl-1,2,3,4-tetrahydrisoquinoline, and at the same time, that the phenolic base formed by the fission of the methylenedioxy group in *dl*-1-(4'-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (V) by the sodium-liquid ammonia process is *dl*-1-(4'-methoxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (VI).

The author expresses his appreciation to Prof. Dr. M. Tomita for his continuing counsel and encouragement in this work. The cost of this investigation was partly met by the Grant in Aid for Scientific Research from the Ministry of Education and is hereby gratefully acknowledged.

Experimental*

(1) **Reduction of O,O-Dimethyl Ether Methyl-Methine (VII) of the A-Base (Formation of 3,4′-Dimethoxy-6-dimethylaminoethyl-α,β-diphenylethane (VIII))**—0.25 g. of O,O-dimethyl ether methyl-methine (VII) of the A-base was dissolved in 10 cc. MeOH and hydrogenated under the atmospheric pressure, in the presence of Pd-black catalyst prepared from 10 cc. of 1% aq. $PdCl_2$, 20 cc. of H_2 being absorbed. After removal of the catalyst and the solvent, the residue was dissolved in water, basified with conc. aq. NH_3 and the depositing base was extracted with ether. The ether solution was dried over anhyd. K_2CO_3 and the solvent removed, leaving a slightly yellowish substance which resisted various attempts at crystallization. This was then dissolved in the minimum of benzene and excess MeI was added, and the mixture was allowed to stand for a while, whereby the methiodide deposited as white needles. Upon recrystallization from abs. EtOH they showed m.p. 146°. *Anal.* Calcd. for $C_{20}H_{27}O_2NI$: C, 55.38; H, 6.59. Found : C, 55.42; H, 6.50.

(2) **Hofmann Degradation of the Hydromethine (VIII) (Formation of 3,4′-Dimethoxy-6-vinyl-α,β-diphenylethane (IX))**—0.1 g. of the above hydromethine (VIII) methiodide was added to 10 cc. of 20% aq. KOH and the mixture was heated on a boiling water bath for 30 mins. After cooling, the deposited oil was taken up in ether, the ether solution was shaken once with 1% aq. HCl, washed with water, and dried over anhyd. K_2CO_3. Removal of the solvent left a colorless oil which in spite of all attempts did not crystallize.

(3) **Oxidation of Des-N-Hydromethine (IX) (Formation of 3,4′-Dimethoxy-α,β-diphenylethane-6-carboxylic Acid (X))**—To a solution of 0.2 g. of the above des-N-hydromethine (IX) in 5 cc. of acetone was added 15 cc. of 5% aq. $KMnO_4$ and the mixture was kept overnight at room temp. Then MnO_2 which formed was decomposed by SO_2 and the oxidation product was taken up in ether. The ether solution was shaken with 5% aq. KOH, and the aq. layer was acidified with conc. aq. HCl, and the deposited product was reextracted with ether. The ether extract, after being washed with water, was dried over anhyd. Na_2SO_4, and the solvent distilled off, yielding a reddish yellow resinous substance, which soon solidified. After vacuum sublimation and subsequent crystallization from a mixture of ether and petr. ether it formed white needles, m.p. 115~116°.

(4) **Decarboxylation of the Carboxylic Acid (X) (Formation of 3,4′-Dimethoxy-α,β-diphenylethane (XI))**—A solution of 0.1 g. of the carboxylic acid (X) in 3 cc. of purified quinoline was boiled gently with a small amount of Cu powder for 15 mins. over a direct flame. After cooling, the content was diluted with 30 cc. of ether and filtered from Cu powder. The filtrate was shaken with 5 portions of 5% aq. HCl followed by 3 portions of 5% aq. NaOH, and dried over anhyd. K_2CO_3. Removal of the solvent left a colorless oil. This was chromatographed in benzene on alumina and the eluate yielded colorless needles, which after recrystallization from abs. EtOH showed m.p. 36~38°.

(5) **3,4′-Dimethoxystilbene-β-carboxylic Acid (XII)**—A mixture of 1.4 g. of 3-methoxybenzaldehyde, 10 cc. of Ac_2O, and 1.9 g. of powdered sodium 4-methoxyphenylacetate was boiled gently in an oil bath (120~130°) for 30 hrs., remaining Ac_2O was decomposed by heating with water, and the resultant AcOH was removed *in vacuo*. Then the reaction product was treated with 5% aq. NaOH and the aq. layer was acidified with conc. aq. HCl. The product which separated out was taken up in ether, the ether extract was dried over anhyd. Na_2SO_4, and the solvent removed, leaving a yellowish crystalline mass, which after recrystallization from abs. EtOH, formed slightly yellowish needles, m.p. 167~168°. *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found : C, 71.54; H, 5.87.

(6) **3,4′-Dimethoxystilbene (XIII)**—A solution of 0.2 g. of the above 3,4′-dimethoxystilbene-β-carboxylic acid (XII) in 5 cc. of purified quinoline was boiled gently with a small amount of Cu powder for 20 mins. over a direct flame. After cooling, the content was treated in the same manner as described in (4), and the slightly yellowish oil obtained solidified to a crystalline mass after standing. This was recrystallized from abs. EtOH to form colorless plates, m.p. 105~107°. *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found : C, 80.03; H, 6.87.

(7) **3,4′-Dimethoxy-α,β-diphenylethane (XI)**—0.8 g. of the above 3,4′-dimethoxystilbene (XIII) was dissolved in 20 cc. MeOH and hydrogenated at atmospheric pressure in the presence of Pd-black catalyst prepared from 10 cc. of 1% aq. $PdCl_2$. A total of 90 cc. of H_2 was absorbed in 3 hrs. Removal of the catalyst and the solvent left an oily residue which was taken up in ether. The ether extract was dried over anhyd. K_2CO_3 and the solvent removed, yielding a slightly yellowish oil. This, after being chromatographed in benzene on alumina, formed colorless needles, which upon recrystallization from abs. EtOH, showed m.p. 36~38°, undepressed on admixture with the decarboxylation product, m.p. 36~38°, described in (4). *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found : C, 78.88, 79.71; H, 7.88, 7.68.

---

* All melting points are uncorrected. The author is indebted to Mr. K. Hozumi and the members of the Microanalytical Laboratory of this Institute for the microanalyses.

Summary

The bisected phenolic base, m.p. 205∼207°(decomp.) (A-base) obtained by the fission of cepharanthine by sodium in liquid ammonia has positively been proved to be *d*-1-(4'-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II).

(Received April 21, 1955)

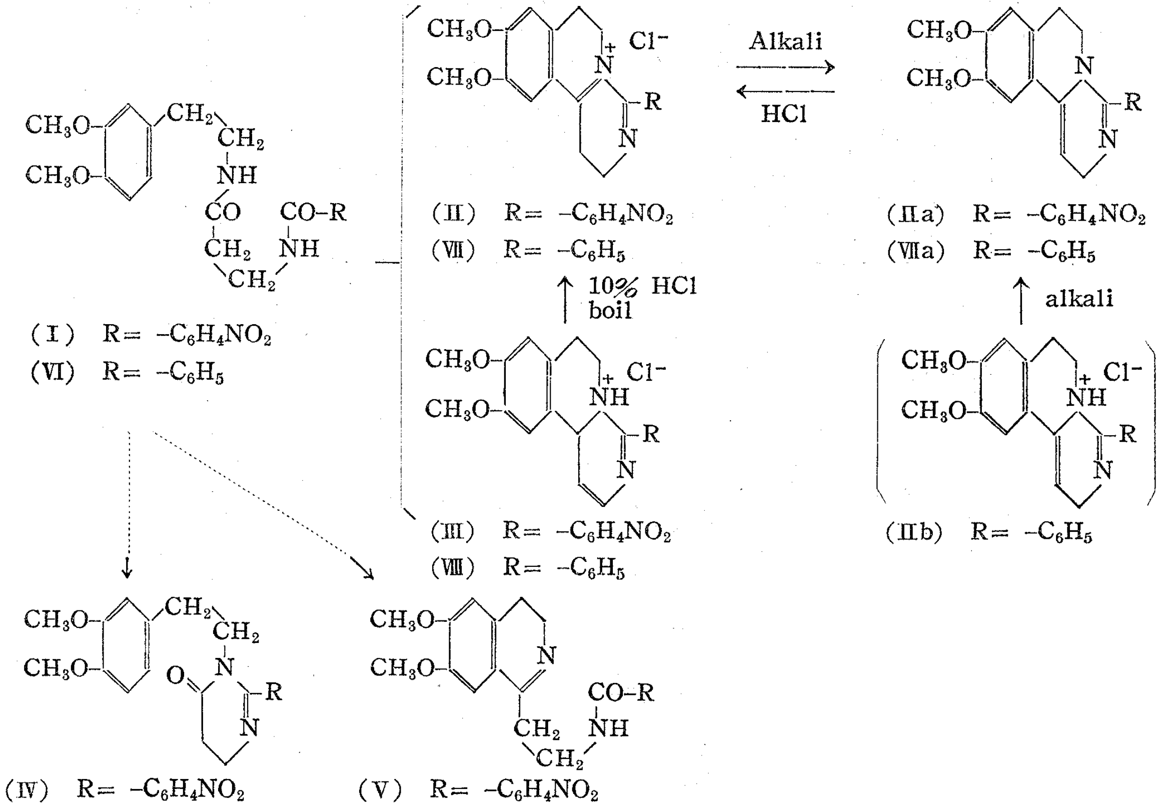
---

49. **Tetsuji Kametani and Toyoyuki Katagi**: Studies on the Syntheses of Isoquinoline Derivatives and their Analogs. XXXV. Migration of the Double Bond of Pyrimidinoisoquinolines and Presumption of their Structures by the Infrared Absorption Spectra.

(*Pharmaceutical Institute, Medical Faculty, University of Osaka**)

In the preceding paper[1] we reported that two kinds of isomers having higher and lower melting point were obtained by the cyclization of N-(*p*-nitrobenzoyl-*β*-alanyl)-*β*-3,4-dimethoxyphenylethylamine (I) by the Bischler-Napieralski reaction. In this paper we present the assumed structure of both substances by the infrared absorption spectra and revealed the migration mechanism of double bond between them.

The hydrochloride with a higher melting point is more difficult to dissolve in water and methanol than the one of lower melting substance and the former was difficult to be purified from methanol and could be recrystallized from hot water or acetic acid. By the results of elemental analysis of both compounds, they corresponded respectively to the calculations of the objective pyrimidinoisoquinoline hydrochloride containing 3 moles



---

* Hotarugaike, Toyonaka, Osaka-fu (亀谷 哲治, 加多木豊之).

[1] Part XXXIV: Kametani, Katagi: J. Pharm. Soc. Japan, **75**, 709(1955)