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PHARMACEUTICAL BULLETIN

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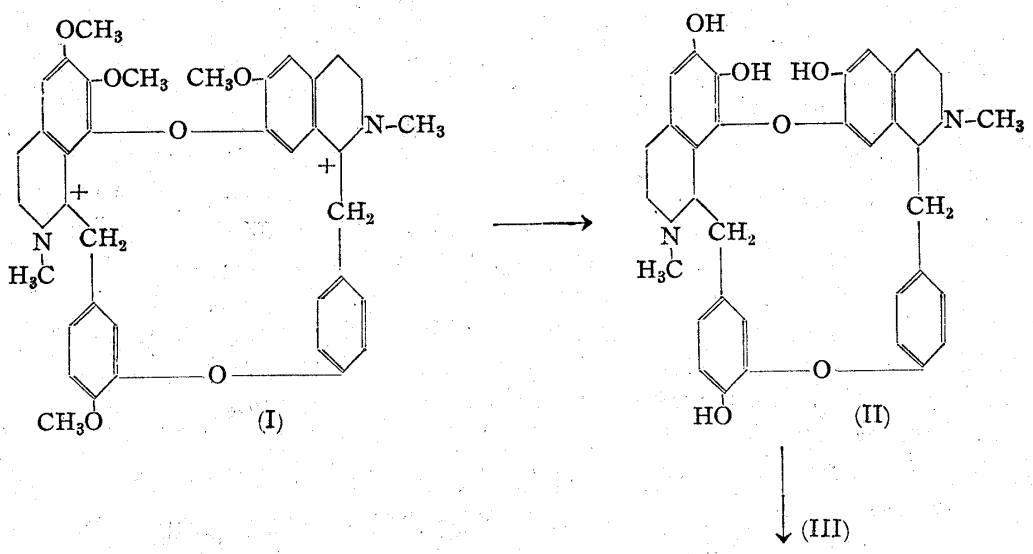
1. Yasuo Inubushi: Studies on the Alkaloids of Menispermaceous Plants. CXIII[1]. On the Structure of Biscoclaurine Alkaloids. (16)[1]. Synthesis of Trilobine-Type Alkaloid from Tetrandrine.*

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

In the previous paper[1] of this series, it was reported by M. Tomita, Inubushi, and Kozuka that by allowing isotetrandrine to react with hydrobromic acid, a new isomer of the trilobine-type bases could be prepared. The present paper describes the results obtained by the same reaction applied to tetrandrine.

Tetrandrine is an alkaloid contained in *Stephania tetrandra* S. Moore (Japanese name "Shima-hasunoha-kazura"), and its chemical constitution was studied by H. Kondo and Yano[2], and subsequently by M. Tomita and E. Fujita[3], who confirmed that it should be represented by formula (I) and that its two centers of asymmetry are (+, +), whereas those of isotetrandrine are (−, +).



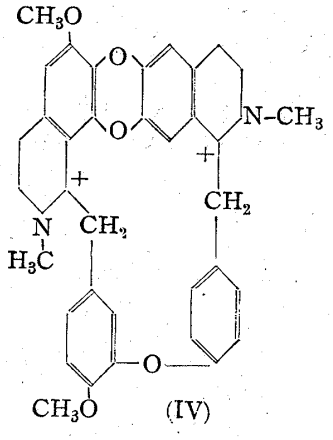
*) Masao Tomita: Studies on the Alkaloids of Menispermaceous Plants. CXIII.

**) Yoshida-konoe-cho, Sakyo-ku, Kyoto (犬伏康夫).

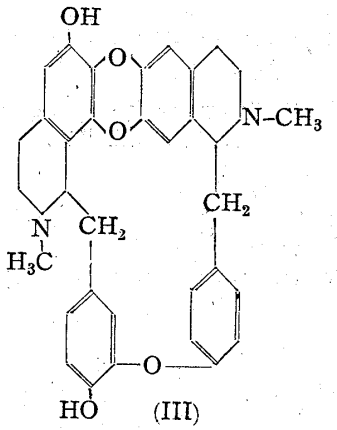
1) M. Tomita, Y. Inubushi, M. Kozuka: Part CXI, CXII. This Bulletin, 1, 360, 368, (1953).

2) H. Kondo, K. Yano: J. Pharm. Soc. Japan, 48, 107 (1928); *ibid.*, 49, 315 (1929); *ibid.*, 50, 224 (1930); *ibid.*, 52, 827 (1932); Ann., 497, 90 (1932); F. v. Bruchhausen, H. Oberembt, A. Feldhaus: *Ibid.*, 507, 114 (1933).

3) M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, 71, 1039 (1951); M. Tomita: Fortschr. Chem. org. Naturstoffe, 9, 175 (1952).



(IV)



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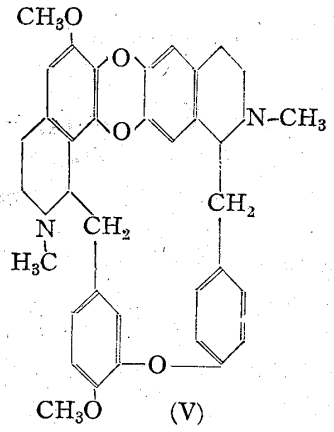

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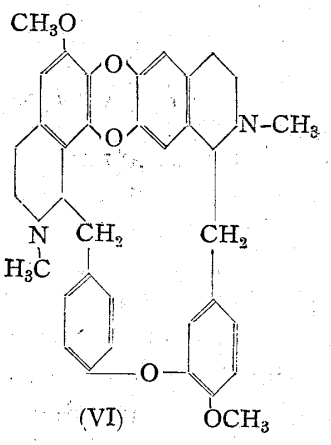

(VI)

On being heated with hydrobromic acid (d=1.78) at 100° for 3 hours, tetrandrine (I) furnished demethyltetrandrine (II), which very finely crystallized and melted with decomposition at 228°, $[\alpha]_D^{18}$: +206.7° (in acetone). It contains no methoxyl groups and gives a green coloration with ferric chloride, changing to violet on addition of alkali. The analytical data reveal the presence of three molecules of water of crystallization which could not be readily removed and correspond to the composition of $C_{34}H_{34}O_6N_2 \cdot 3H_2O$. The data of this compound are in good agreement with those of the corresponding one, already prepared by H. Kondo and Yano[4].

Demethyltetrandrine (II) was further heated with hydrobromic acid (d=1.78) in a sealed tube at 130° for 3 hours, and gave anhydrodemethyltetrandrine (III). This compound forms microscopic crystals with m.p. 275° (decomp.), $[\alpha]_D^{15}$: +335.5° (in alcohol). It is phenolic, but gave no coloration with ferric chloride, and a positive test for diphenylene dioxide nucleus with sulfuric-nitric acid reagent. The analytical figures represent the composition of $C_{34}H_{32}O_5N_2 \cdot 1^1/_2H_2O$. Mild acetylation of this substance with acetic anhydride yielded pillar-shaped crystals, m.p. 272~274°, possessing basicity, which correspond to the diacetate by analyses.

Anhydrodemethyltetrandrine (III) was converted by methylation with diazomethane into O-methylanhydrodemethyltetrandrine (IV), which crystallized in the form of slender pillars, m.p. 244~247°, $[\alpha]_D^{28}$: +449° (in chloroform). It showed two methoxyl groups by the Zeisel estimation, and its composition corresponds to $C_{36}H_{36}O_5N_2$. It gave

4) H. Kondo, K. Yano: J. Pharm. Soc. Japan, 49, 315 (1929); *ibid.*, 50, 224 (1930); *ibid.*, 52, 827 (1932); Ann., 497, 90 (1932).

a positive test for diphenylene dixoide nucleus, and also showed quite the same color reactions as those for trilobine or isotrilobine.

The ultraviolet absorption spectra of tetrandrine (I) and demethyltetrandrine (II) present complete similarity to those of the oxyacanthine-berbamine type of bases, as is also the case with the absorption spectra of the corresponding substances derived from isotetrandrine. Anhydrodemethyltetrandrine (III) and O-methylanhydrodemethyltetrandrine (IV) show the same type of absorption spectra as the trilobine-isotrilobine type of bases (See Figs. 1 and 2).

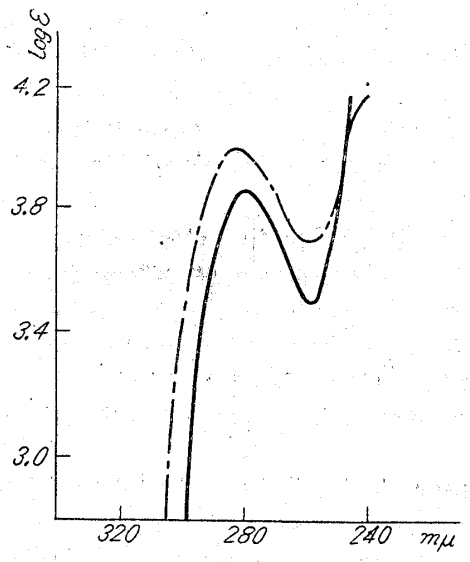

Fig. 1.
—— Tetrandrine
–·– Demethyltetrandrine

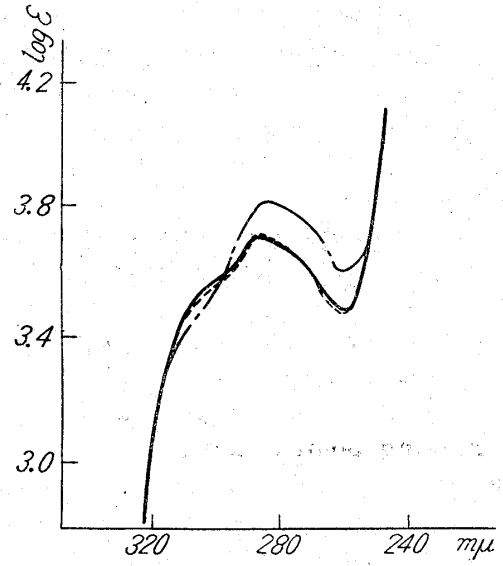

Fig. 2.
—— Trilobine, Isotrilobine
–·– Anhydrodemethyltetrandrine
····· O-Methylanhydrodemethyltetrandrine

Also the infrared spectrum of O-methylanhydrodemethyltetrandrine (IV) belongs to the same type as that of trilobine or isotrilobine.

Comparison of the data of O-methylanhydrodemethyltetrandrine (IV (+, +)), O-methylanhydrodemethylisotetrandrine (IV (−, +)), trilobine, and isotrilobine ((V) and (VI), or *vice versa*) is given in Table I.

Table I.

Trilobine (V or VI)	Isotrilobine (V or VI)	O-Methylanhydrodemethylisotetrandrine (IV (−, +))	O-Methylanhydrodemethyltetrandrine (IV (+, +))
Pillars or Needles m.p. 238° $[\alpha]_D^9$: +302.8° ($CHCl_3$) $C_{36}H_{36}O_5N_2$	Pillars or Needles m.p.213~215° $[\alpha]_D^8$: +314.8° ($CHCl_3$) $C_{36}H_{36}O_5N_2$	Pillars m.p. 272~274° $[\alpha]_D^{24}$: +66.8° ($CHCl_3$) $C_{36}H_{36}O_5N_2$	Pillars m.p. 244~247° $[\alpha]_D^{28}$: +449.7° ($CHCl_3$) $C_{36}H_{36}O_5N_2$
Demethyltrilobine[5]	Demethylisotrilobine[5]	Anhydrodemethylisotetrandrine[1]	Anhydrodemethyltetrandrine (III)
Plates m.p. 290° (decomp.) $[\alpha]_D^{18}$: +229.3° (CH_3CO_2H) $C_{34}H_{32}O_5N_2$	Microscopic crystals m.p. 270° (decomp.) $C_{34}H_{32}O_5N_2$	Needles m.p. 290° (decomp.) $[\alpha]_D^6$: +61.4° (pyridine) $C_{34}H_{32}O_5N_2$	Microscopic crystals m.p. 275° (decomp.) $[\alpha]_D^{15}$: +335.5° (C_2H_5OH) $C_{34}H_{32}O_5N_2$

5) H. Kondo, M. Tomita: J. Pharm. Soc. Japan, 48, 659 (1928); M. Tomita: *Ibid.*, 50, 1035 (1930); H. Kondo, M. Tomita: *Ibid.*, 52, 856 (1932); Ann., 497, 104 (1932).

Acetate	Acetate	Acetate	Acetate
Needles	Needles	Needles	Pillars
m.p. 210°	m.p. 164~166°	m.p. 210°	m.p. 274° (decomp.)
$[\alpha]_D^{24}$: +302.1° ($CHCl_3$)		$[\alpha]_D^{24}$: +118.6° ($CHCl_3$)	
$C_{38}H_{36}O_7N_2$	$C_{38}H_{38}O_7N_2$	$C_{36}H_{36}O_7N_2$	$C_{38}H_{36}O_7N_2$

For the sake of confirmation, O-methylanhydrodemethyltetrandrine (IV), m.p. 244~247°, was fused with trilobine (V or VI), m.p. 237°, and the melting point depressed to 215~225°, showing the two to be not identical. Since there is no doubt that the substance (IV) derived from tetrandrine is a base belonging to the trilobine-isotrilobine series, it is suggested that it must be an isomer of the latter bases.

The difference between O-methylanhydrodemethyltetrandrine and O-methylanhydrodemethylisotetrandrine consists in that although both bases have the same structure (IV), the two centers of asymmetry in the former are (+, +), whereas those in the latter are (−, +), and hence it is clear that the two bases are optically isomeric with each other.

Anhydrodemethyltetrandrine (III) was converted by methylation with dimethyl sulfate in the presence of alkali into the O-methyl ether methyl methosulfate, which in turn was subjected to the first stage of Hofmann degradation, and furnished two kinds of methine bases, a product of m.p. 222° and a product which forms a crystalline hydrobromide, m.p. 50~60° (hydrate). Their identification with two kinds of methine bases obtained from O-methylanhydrodemethylisotetrandrine was established by the mixed melting point determination.

As stated above, the fact that the anhydro-bases derived from isotetrandrine and tetrandrine furnished the same pair of optically active methine bases may be well understood by taking into consideration that at the first stage of Hofmann degradation, the left hand center of asymmetry in O-methylanhydrodemethylisotetrandrine (−, +) and O-methylanhydrodemethyltetrandrine (+, +) was removed by elimination.

The author gratefully acknowledges Prof. Dr. M. Tomita for his continued guidance and to Dr. H. Kondo of ITSUU Laboratory, Tokyo, for the gift of tetrandrine. The author also wishes to extend his appreciation to the Ministry of Education for the grant of Scientific Research Fund.

Experimental[6]

Demethyltetrandrine (II)—One g. of tetrandrine was heated with 20 cc. of hydrobromic acid (d=1.78) at 100° for 3 hrs. After the completion of the reaction the content was poured into 300 cc. of water, when the hydrobromide deposited. Recrystallization of this from aqueous methanol yielded 0.8 g. of needles, m.p. 275°. A solution of the hydrobromide in aqueous methanol was neutralized by aqueous ammonia, and first deposited a small quantity of brown insoluble material, which was removed by filtration. The remaining mother liquor was alkalized by treating with an additional amount of aqueous ammonia, and diluted by a large amount of water, whereupon a yellow precipitate was obtained. This was recrystallized from aqueous methanol to form microscopic crystals, m.p. 228°, weighing 0.6 g. This substance gave a green color with ferric chloride, which on addition of alkali changed to violet. It contains no methoxyl group. $[\alpha]_D^{15}$: +206.7° (in acetone, l=0.3 dm., c=0.22). *Anal.* Calcd. for $C_{34}H_{34}O_6N_2 \cdot 3H_2O$: C, 65.80; H, 6.45. Found: C, 65.43; H, 6.41.

Anhydrodemethyltetrandrine (III)—0.8 g. of demethyltetrandrine (II) was heated with 5 cc. of hydrobromic acid (d=1.78) in a sealed tube at 130~135° for 3 hrs., after which the content was poured into water and the hydrobromide separated out. A suspension of the hydrobromide in alcohol was alkalized with aqueous ammonia, warmed gently, and diluted by a large amount of water to obtain a yellow precipitate. This was purified by reprecipitation from aqueous methanol and crystallized in microscopics, m.p. 275° (decomp., after shrinking at 210°); yield, 0.5 g. It gave no coloration with ferric chloride. The test for diphenylene dioxide nucleus was positive. $[\alpha]_D^{15}$: +335.4° (in alcohol, l=0.3 dm., c=0.16). *Anal.* Calcd. for $C_{34}H_{32}O_5N_2 \cdot 1\frac{1}{2}H_2O$: C, 70.95; H, 6.08. Found: C, 70.87; H, 6.02.

6) All melting points are uncorrected. The author is indebted to Messrs. Hozumi and Imaeda, and to Miss Iwata for the microanalyses.

O-Methylanhydrodemethyltetrandrine (IV)—To a solution of 0.45 g. of anhydrodemethyltetrandrine (III) was added an ether solution of diazomethane prepared from 2 g. of nitrosomethylurea and the mixture was allowed to stand for 2 days. This process was repeated once more, after which the depositing insoluble impurities were removed by filtration, and the solvent distilled off, leaving 0.5 g. of an oily substance. This was dissolved in benzene, and after removal of insoluble materials, passed through an alumina column (1×5 cm.). The initial eluate fraction gave a colorless oil which on addition of acetone crystallized in the form of pillars, weighing 0.21 g. Recrystallization was effected from acetone; m.p. 244~247°. It gave a blue color with sulfuric-nitric acids. Admixture with trilobine (m.p. 235~238°) gave a depression, melting at 215~225°. $[\alpha]_D^{28}$: +449.7° (in chloroform, l=0.3 dm., c=0.33). *Anal.* Calcd. for $C_{36}H_{36}O_5N_2$: C, 74.96; H, 6.30; OCH_3, 10.76. Found: C, 75.18; H, 6.45; OCH_3, 10.97.

Hofmann Degradation of Anhydrodemethyltetrandrine (III)—To a solution of 0.15 g. of anhydrodemethyltetrandrine in 5 cc. of 1% potassium hydroxide was added with stirring 0.8 g. of dimethyl sulfate in small portions and a potassium hydroxide solution at a rate that maintained the reaction mixture alkaline. The reaction mixture was shaken with ether to remove the excess dimethyl sulfate, diluted with water to 25 cc., and treated with 4.5 g. of potassium hydroxide. Then the mixture was heated in a boiling water bath for 30 minutes and after cooling, the depositing oil was taken up in ether. The ether solution was dried over anhydrous potassium carbonate and the solvent removed. Addition of a small amount of acetone to the residue gave the crystals having the m.p. of 222°, undepressed on admixture with the crystals, m.p. 222°, obtained by the Hofmann degradation of anhydrodemethylisotetrandrine. The mother liquor filtered from the above crystals was freed of the solvent, and on addition of diluted hydrobromic acid solution, gave rise to a crystalline hydrobromide, m.p. 50~60°.

Anhydrodemethyltetrandrine Acetate—0.06 g. of anhydrodemethyltetrandrine (III) was heated with 1 g. of acetic anhydride at 60° for 30 minutes. After cooling, the reaction mixture was diluted with water, neutralized with aqueous potassium carbonate, and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, and the solvent removed. The residue was recrystallized from a mixture of alcohol and a small portion of chloroform to rectangular pillars, m.p. 274° (decomp.). Yield, 0.02 g. *Anal.* Calcd. for $C_{38}H_{36}O_7N_2 \cdot H_2O$: C, 70.2; H, 5.8. Found: C, 69.86; H, 5.97.

Summary

In the preceding paper of this series it was reported that an attempt to synthesize an alkaloid of the trilobine type from isotetrandrine, belonging to the oxyacanthine-berbamine series, was found successful. In the present paper, the synthesis of O-methylanhydrodemethyltetrandrine (IV), belonging to the trilobine type, from tetrandrine (I), an optical isomer of isotetrandrine, is described and their chemical properties comparatively examined.

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