

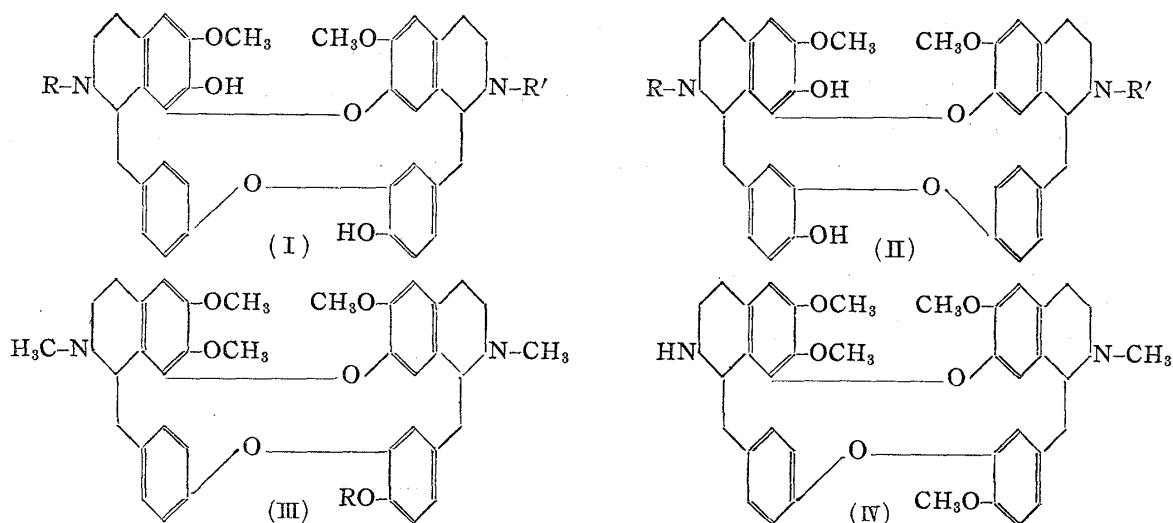
76. Yasuo Inubushi: Studies on the Alkaloids of Menispermaceous Plants. CXXVII.¹⁾ Structure of Trilobamine (Daphnoline).*

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Trilobamine was first described by Kondo and Tomita²⁾ who isolated it, together with trilobine and isotrilobine, from a Menispermaceous plant, *Cocculus trilobus* DC. (Japanese name "Aotsuzura-fuji"), and by oxidation and Hofmann degradation, showed its O,O,N-trimethyl methiodide to be identical with O-methoxyacanthine methiodide.

In 1914, Pyman³⁾ recorded the isolation of an alkaloid, daphnoline, from the bark of an Australian tree *Daphnandra micrantha*, but he made no study of its constitution. Later, Bick and Whalley,⁴⁾ and Bick, Ewen, and Todd⁵⁾ isolated the same alkaloid from *Daphnandra aromatica* and *Daphnandra micrantha*, and elucidated as a result of comparative studies that daphnoline and trilobamine were identical and that both have the structure (I), in which one of R and R' is H and the other Me, or (II), in which one of R and R' is H and the other Me.

Since the recent work⁶⁾ on the fission of O-methoxyacanthine with sodium in liquid ammonia has revealed that oxyacanthine has the structure (III; R=H), it follows that trilobamine should be represented by formula (I). However, it has still remained unsettled which of R and R' in formula (I) represents Me and which H.



A new supply of trilobamine from the mother-liquor of trilobine and isotrilobine being now available, the author examined this problem further, which forms the subject of the present paper.

Among the alkaloids known as having the structure (I), hydroepistephanine-A,⁷⁾

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1) Part CXXVI. Y. Sasaki: This Bulletin, **3**, 250(1955).

2) H. Kondo, M. Tomita: Arch. Pharm., **269**, 433(1931); J. Pharm. Soc. Japan, **51**, 451(1931); *Ibid.*, **55**, 646(1935).

3) F. E. Pyman: J. Chem. Soc., **1914**, 1619.

4) I. R. C. Bick, T. G. Whalley: Univ. Queensland Papers, Dept. Chem., **1**, No. 33, 7(1948).

5) I. R. C. Bick, E. S. Ewen, A. R. Todd: J. Chem. Soc., **1949**, 2767.

6) E. Fujita: J. Pharm. Soc. Japan, **72**, 213, 217(1952).

7) H. Kondo, K. Tanaka: *Ibid.*, **63**, 273(1943).

obtainable by reduction of epistephanine,⁸⁾ an alkaloid of *Stephania japonica* Miers (Japanese name "Hasunoha-kazura"), is the only alkaloid, whose structure has very recently been established by Tomita and Fujita⁹⁾ as having the structure (IV).

Comparison of the properties of O,O-dimethyltrilobamine hydrochloride with those of hydroepistephanine-A hydrochloride is made in Table I.

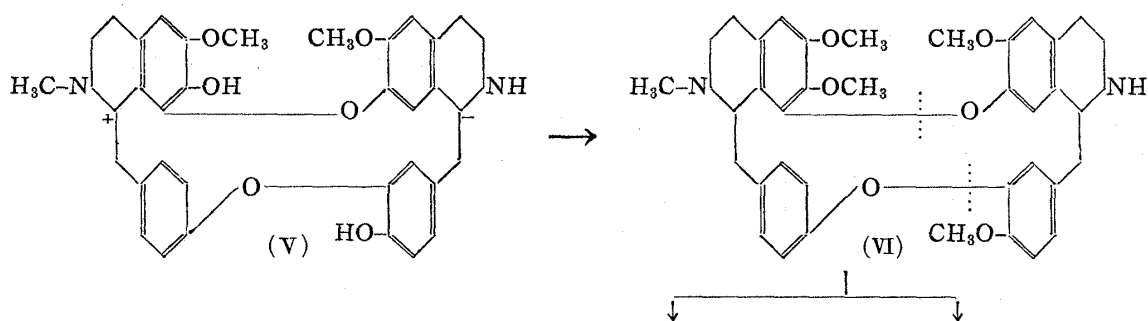
TABLE I.

	m.p.	$[\alpha]_D$
O,O-Dimethyltrilobamine hydrochloride	258~260°(decomp.)	+272.2°(H ₂ O)
Hydroepistephanine-A hydrochloride	259~260°(decomp.)	+299.3°(H ₂ O)

In fact, these two bases resemble each other closely in their physical properties, but in the determination of their infrared spectra there was observed some difference in the finger print regions, which revealed that they were not identical. This fact led us to the conclusion that the structure of trilobamine corresponds to formula (I) in which R is Me and R' is H, but in order to confirm this, attempt was made to apply the reductive fission with sodium in liquid ammonia to trilobamine.

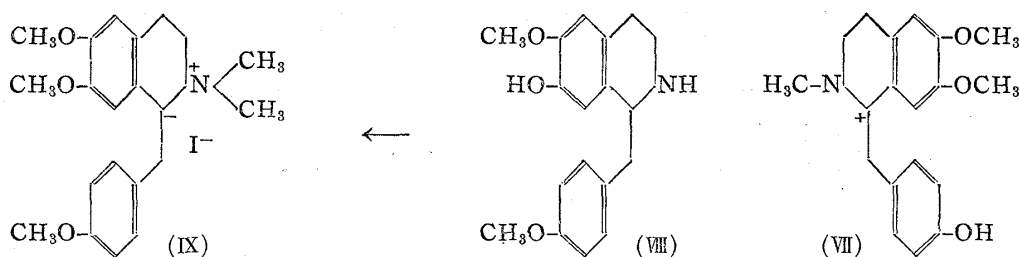
By methylation with diazomethane trilobamine was first converted into its O,O-dimethyl ether and the latter was submitted to this fission in the usual manner. The ethanolic solution of the bisected bases obtained was treated with an ethanolic solution of oxalic acid, yielding the oxalate. The oxalate showed m.p. 211~212°(efferv.) after recrystallization from ethanol, and the free base was obtained as m.p. 144~145°, $[\alpha]_D^{18}$: +116.7°(in CHCl₃), undepressed on admixture with *d*-armepavine (VII). Subsequent treatment of the mother-liquor from the above oxalate yielded the hydrochloride of (VIII) as rhombics, m.p. 241~242°, $[\alpha]_D^{18}$: +80.1°. It gave a positive Liebermann's nitroso reaction, and contains two methoxys and no methylimino group. The free base from this hydrochloride formed needles, m.p. 96~98°, which, because of the small amount available, was converted immediately into its methiodide by methylation with alkali and methyl iodide. The methiodide, when recrystallized from a mixture of methanol and ether, showed m.p. 135~136°(sint. at 128°), $[\alpha]_D^{20}$: -68.9°, undepressed by admixture with *l*-O-methylarmepavine methiodide. The sample of *d*-O-methylarmepavine methiodide depressed the m.p. to 113~130°.

These experimental results indicate that on fission with sodium in liquid ammonia, O,O-dimethyltrilobamine (VI) was bisected into two coclaurine units, of which one is *l*-1-(4'-hydroxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (*d*-armepavine) (VII) and the other, 1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (VIII). In addition it is interesting to note that while the hydrochloride of (VIII) was obtained as dextrorotatory, it underwent change to the levorotatory compound, viz. *l*-1-(4'-methoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline methiodide (*l*-O-methylarmepavine methiodide) (IX) during methylation with alkali and methyl iodide.



8) H. Kondo, T. Sanada: *Ibid.*, **47**, 177, 930(1927); **48**, 1141(1928).

9) M. Tomita, E. Fujita: *This Bulletin*, **2**, 378(1954).



Thus, it has become certain that trilobamine (daphnoline) has the structure (V) belonging to the oxyacanthine series and that the stereochemical arrangements about the two asymmetric centers are identical with those of oxyacanthine. As expected, the methylimino group of trilobamine is situated at the right hand tetrahydroisoquinoline ring of (V), which is reverse of that of hydroepistephanine (IV).

With regard to the position of one phenolic hydroxyl group present in the isoquinoline ring of trilobamine no direct evidence has been provided as yet, but as suggested by Kondo and Tomita²⁾ from the biogenetic consideration of the biscoclaurine-type bases, it would seem most plausible to assume that it is located at 7-position of the left hand isoquinoline ring in formula (V).

The author wishes to acknowledge his indebtedness to Professor M. Tomita for his interest in this work and to thank Dr. H. Kondo, Dr. M. Satomi, and Mr. K. Takeda of the ITSUU Laboratory in Tokyo for the gift of a sample of hydroepistephanine-A and to Messrs. Y. Matsui and M. Narisada of the Research Laboratory, Shionogi & Co., Ltd. for the measurement of the infrared spectra. This research was supported in part by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which the author is also grateful.

Experimental¹⁰⁾

Isolation of Trilobamine—From EtOH solution containing the total tertiary bases from *Cocculus trilobus* DC., trilobine and isotrilobine were removed as their crystalline hydrobromides. HBr solution which remained was made alkaline with NH_4OH , and then diluted with a large amount of water, depositing a gray precipitate. It was dissolved in dil. aq. AcOH, made alkaline with aq. NaOH, and the depositing non-phenolic base was taken up in ether. The aq. NaOH solution free from the non-phenolic base, after being acidified with dil. H_2SO_4 , was made alkaline with K_2CO_3 , and the phenolic base which separated out was extracted with $CHCl_3$. The $CHCl_3$ extract, after being dried over anhyd. K_2CO_3 , was concentrated somewhat, depositing colorless elongated monoclinic prisms. By recrystallization from MeOH, they showed m.p. 195° (efferv. at 212°). Yield, 0.5 g. (trilobamine). *Anal.* Calcd. for $C_{35}H_{36}O_6N_2 \cdot CHCl_3$: C, 61.71; H, 5.28. Found: C, 61.36; H, 4.92.

Meanwhile, the $CHCl_3$ mother-liquor from trilobaime was evaporated and the residue was induced to crystallize from a mixture of EtOH and acetone. The crude normenisarine thus obtained was recrystallized from the same solvent mixture to form minute pillars, m.p. 223° (decomp.). Yield, 0.8 g.

Methylation of Trilobamine with Diazomethane; O,O-Dimethyltrilobamine (VI)—To a suspension of 0.5 g. of trilobamine in EtOH was added an ethereal solution of CH_2N_2 and the mixture was set aside. After 2 days, the solution, which had become clear, was evaporated, and the residue was dissolved in dil. AcOH, made alkaline with aq. NaOH, and the depositing base was taken up in ether. The ethereal extract was dried over anhyd. K_2CO_3 , and the solvent removed, yielding an amorphous residue. This was converted into its crystalline hydrochloride by dissolving it in EtOH and making the solution acid with a few drops of HCl. Needles, m.p. $258\sim 260^\circ$ (decomp.). Yield, 0.35 g. $[\alpha]_D^{20}$: $+272.2^\circ$ (in H_2O , $l=0.5$ dm., $c=0.47$). *Anal.* Calcd. for $C_{37}H_{40}O_6N_2 \cdot 2HCl \cdot 2H_2O$: C, 61.87; H, 6.13. Found: C, 61.81; H, 6.49.

Cleavage Reaction of O,O-Dimethyltrilobamine by Metallic Sodium in Liquid Ammonia—A solution of 0.3 g. of O,O-dimethyltrilobamine (VI) in ether and Na were added alternately in small portions to a vigorously stirring liquid NH_3 . After completion of the reaction, the mixture was allowed to stand to permit evaporation of NH_3 , and the residue was separated into a

10) All melting points are uncorrected. The microanalyses were carried out by Mr. K. Hozumi and the members of the Microanalytical Laboratory of this Institute, to whom the author is grateful.

non-phenolic and a phenolic portion in the usual manner. There was obtained no detectable amount of a base from the non-phenolic portion.

Treatment of the Bisected Phenolic Base—The crude oily phenolic base was dissolved in a small amount of EtOH, and a saturated EtOH solution of oxalic acid added. The solution was kept standing and the oxalate deposited as crystals. Recrystallization from a mixture of MeOH and EtOH yielded 0.07 g. of colorless needles, m.p. 211~212°(efferv.). The free base from the oxalate formed needles, m.p. 144~145°, undepressed on admixture with *d*-armepavine (VII). $[\alpha]_D^{18}$: +116.7°(in CHCl₃, *l*=0.5 dm., *c*=0.5). *Anal.* Calcd. for C₁₉H₂₈O₃N: C, 72.82; H, 7.40. Found: C, 72.84; H, 7.48.

On the other hand, the mother liquor separated from the above oxalate was freed from EtOH, and the residue was dissolved in a small amount of water, made alkaline with NH₄OH, and extracted with ether. The ethereal extract was dried over anhyd. K₂CO₃, and the ether evaporated. The residue was dissolved in a small amount of EtOH, and a few drops of HCl added. Then ether was added to the solution, whereupon rhombic crystals (VIII; hydrochloride), m.p. 241~242°, deposited out slowly. Yield, 0.03 g. Liebermann's nitroso reaction was positive. $[\alpha]_D^{18}$: +80.1°(in CHCl₃, *l*=0.5 dm., *c*=0.5). The free base from the hydrochloride was obtained as needles, m.p. 96~98°, which, because of the small amount available, was difficult to purify. Attempt was therefore made to characterize it as the methiodide. The above free base was refluxed in MeOH(20 cc.) with 0.5*N* methanolic KOH (1 cc.) and excess MeI for 6 hrs. Then a similar amount of 0.5*N* KOH and MeI were added, and the mixture was refluxed for a further 3 hrs. The solvent and excess MeI were removed under reduced pressure and the crude methiodide was crystallized by treatment with aq. MeOH. This was recrystallized several times from a mixture of MeOH and ether. Colorless needles were obtained, which melted at 134~136°(sint. at 128°). $[\alpha]_D^{20}$: -68.9°(in EtOH, *l*=0.5 dm., *c*=0.46). When this methiodide was fused with *l*-O-methylarmepavine methiodide (IX), m.p. 135~136°(sint. at 130°), no m.p. depression was observed, and with *d*-isomer, m.p. 135~136°(sint. at 128°), obvious m.p. depression occurred (113~130°). Consequently, it was found that the methiodide obtained by the fission of O,O-dimethyl-trilobamine was identical with *l*-O-methylarmepavine methiodide (IX).

Summary

The structure of trilobamine (daphnoline) was so far considered as being represented by formula (I) (one of R and R' is H and the other CH₃).

As a result of the fission of O,O-dimethyltrilobamine by the sodium-liquid ammonia procedure, it has become unambiguous that trilobamine (daphnoline) has structure (V).

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