2. Masao Tomita and Yasuo Inubushi: Studies on the Alkaloids of Menispermaceous Plants. CXIV. On the Structure of Trilobine and Isotrilobine. (10)[1]

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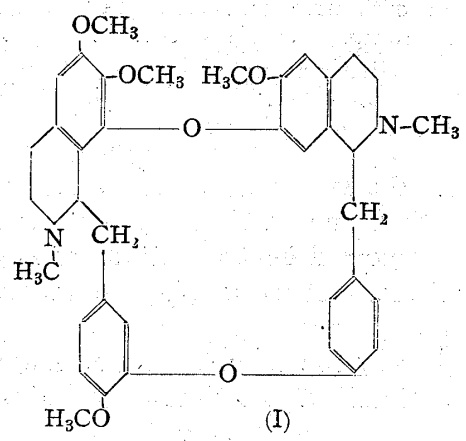
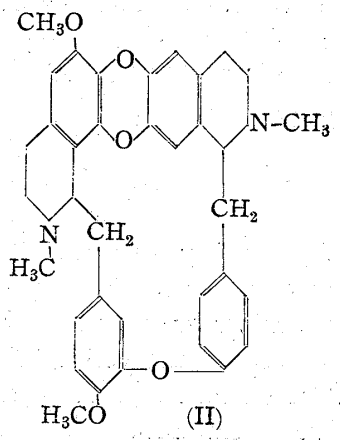
In the preceding papers of this series, it was shown that the bases of the trilobine-isotrilobine type, possessing a diphenylene dioxide group in their molecules, were derived from isotetrandrine (I (−, +))[2] and tetrandrine (I (+, +))[2] belonging to the oxyacanthine-berbamine series, and that O-methylanhydrodemethylisotetrandrine (II (−, +))[3] and O-methylanhydrodemethyltetrandrine (II (+, +))[4] thereby obtained were both assumed to be the isomers of either trilobine or isotrilobine ((II) or (IV)), or *vice versa*). It was also revealed that the methine bases obtained by Hofmann degradation of these bases were both optically active, and not identical with the inactive methine bases derived from trilobine and isotrilobine.

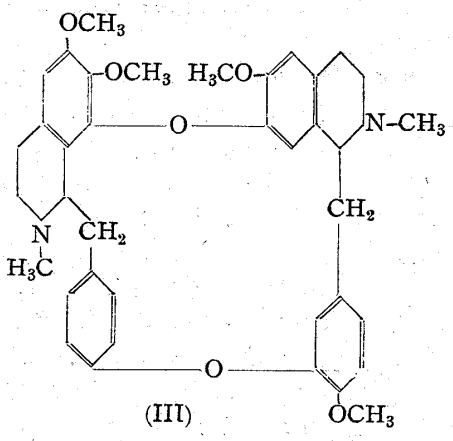
From the various results of this series of studies, it seems most likely that O-methylanhydrodemethyltetrandrine derived from tetrandrine (I (+, +)) is a base whose structure may well be represented by formula (II (+, +)). Meanwhile, it has been



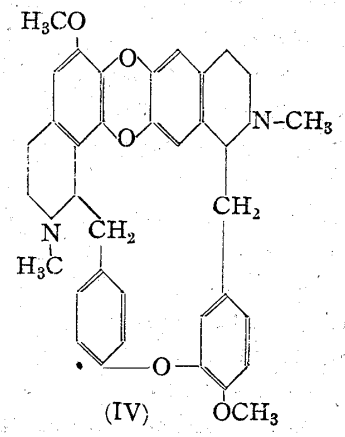
(I)



(II)



(III)



(IV)

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1) Part (9): T. Tani: J. Pharm. Soc. Japan, 62, 481 (1942).
2) (+, +) or (−, +) indicates the signs of the rotations of the two asymmetric centers.
3) M. Tomita, Y. Inubushi, M. Kozuka: Part CXI: This Bulletin, 1, 360 (1953).
4) M. Tomita, Y. Inubushi: Part CXIII: *Ibid.*, 2, 1 (1954).

suggested from our earlier investigations that since trilobine and isotrilobine ((II) and (IV), or *vice versa*) show the specific rotations of the same value of ca. +300°, both bases must be structurally isomeric with each other. Accordingly, it seems reasonable to assume that O-methylanhydrodemethyltetrandrine should be identical with either trilobine or isotrilobine. Contrary to our expectations, however, as was described in the earlier paper[4] of this series, it was found that these bases as well as their methine bases are not identical, though they have a very close relationship with each other.

Consideration on the bases of the foregoing experimental results leads to a conclusion that trilobine ($[\alpha]_D^9$: +302.8°) and isotrilobine ($[\alpha]_D^8$: +314.8°) are not such bases as can be derived from the berbamine type of bases (I), such as tetrandrine (I (+, +)) or isotetrandrine (I(−, +)), but both must have the structures of (IV) type, derivable from the oxyacanthine type of bases (III). If trilobine and isotrilobine both belong to the bases of (IV) type, it may well be assumed that the two asymmetric centers in the molecules of these bases are not (+, +) or (−, −), but must be (+, −) or (−, +), considering from the values of their specific rotations. In other words, it follows that the relationship between trilobine and isotrilobine is not that of structural isomerism, but of diastereoisomerism. Thus, the final conclusion arrived at is that if these bases are postulated to constitute an optical isomer derivable from the oxyacanthine series, then the optically inactive methine bases derived from these bases should be identical. From the point of such a view, it became necessary to reinvestigate each of trilobine methyl methines of needles, m.p. 106°[5], and m.p. 105~107°[6], $[\alpha]_D$: ±0° (hydrochloride: needles, m.p. 260° (decomp.); methiodide: pillars, m.p. 260° (decomp.)) and isotrilobine methyl methines of needles, m.p. 115°[5], and m.p. 110~114°[6], $[\alpha]_D$: ±0° (hydrochloride: needles, m.p. 265° (decomp.); methiodide: pillars, m,p. 264° (decomp.)).

Prior to this, one of the authors, M. Tomita[5], reported in his studies on the structures of trilobine and isotrilobine, that in view of the fact that these bases have the specific rotations of the same value of ca. +300°, and their inactive methine bases show a slight but appreciable difference of 9° in their melting points, trilobine and isotrilobine should be structurally isomeric with each other without comparing them directly by the mixed melting point determination.

The samples of trilobine methyl methine and isotrilobine methyl methine reserved by us were reëxamined first. The former showed m.p. 105~107° and the latter, m.p. 113~115°, the discrepancy of approximately 9° being recognized between them. However, a mixed melting point of these samples showed no depression, melting at 105~115°. Then, the sample of trilobine methyl methine (m.p. 105~107°) was purified through its hydrochloride, chromatographed on alumina as a benzene solution, and recrystallized from acetone. The purified sample thus obtained, crystallizing in pillars, showed m.p. 108~110°, but after completely drying *in vacuo* for a long time, its melting point was raised to 113~115°. As a result, the sample of trilobine methyl methine, m.p. 105~107°, described in the litetrature[5,6], was found to be in a state of incomplete drying, and hence it should be corrected as m.p. 113~115°. On the other hand, the sample of isotrilobine methyl methine, m.p. 113~115°, immediately after recrystallization from acetone, showed m.p. 108~114°, but on drying *in vacuo* for many hours, the melting point was raised to 113~115°. Admixture of these methine bases showing the same melting point of 113~115° showed no depression, melting at 113~115°. The identity of these methine bases (after complete drying) was also confirmed by X-ray powder photography and infrared spectrum. The foregoing results reveal that trilobine methyl methine and isotrilobine methyl methine are identical and the sample of trilo-

5) H. Kondo, M. Tomita: J. Pharm. Soc. Japan, 52, 356 (1932); Ann., 497, 104 (1932).
6) M. Tomita, T. Tani: J. Pharm. Soc. Japan, 62, 468 (1942).

bine methyl methine with the m.p. 106°, described earlier in the literature, was in a state of incomplete drying. This substance is considered to hold solvent of crystallization tenaciously which cannot readily be removed unless it is dried *in vacuo* for a long period of time.

A similar evidence may be afforded by an X-ray powder photography. Namely, both trilobine methyl methine and isotrilobine methyl methine, when in a state of incomplete drying, show no marked ring, owing to the tenacious retention of solvent of crystallization, but after having been thoroughly dried for seven days, they both show the same marked ring.

By the foregoing experimental results, such a view, as so far held, that trilobine and isotrilobine should be represented by (II) and (IV) or *vice versa*, and be structurally isomeric with each other, just as the oxyacanthine type of bases (III) are with the berbamine type of bases (I), must be altered, because trilobine and isotrilobine are assumed to constitute the optical isomers which can be represented by the same structural formula (IV), by comparing directly the inactive methine bases derived from the above original bases, and the difference between them is considered to be that in the steric configurations of their two asymmetric centers, those of the one are (+, −) and the other, (−, +).

At an earlier date, Fujita[7] carried out a cleavage reaction on O-methyloxyacanthine (V) ($[\alpha]_D$: +270° in chloroform) by metallic sodium in liquid ammonia and gained *d*-armepavine (VI) and a phenolic bisected base, by methylation of which he proved it to be *l*-O,O,N-trimethylcoclaurine (VII). Subsequently, the same investigator[8] applied the same reaction to O-methylrepandine (V) ($[\alpha]_D^{23}$: −80.4° in chloroform), and as a result, obtained *d*-armepavine (VI) and a phenolic bisected base, which was confirmed by methylation to be *d*-O,O,N-trimethylcoclaurine (VII).

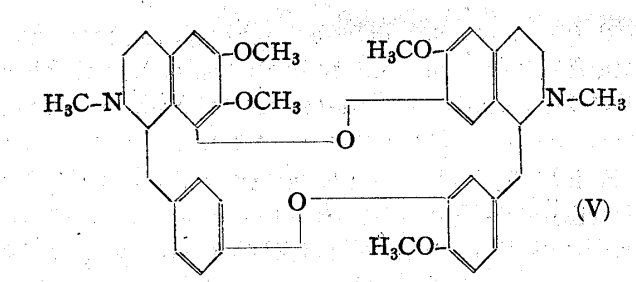
Tomita and Sasaki[9] submitted cepharanthine (VIII) ($[\alpha]_D$: +300° in chloroform) to the same mode of cleavage reaction and gained two phenolic bases, by methylation of which they proved them to be the substance (IX) corresponding to *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline, and *l*-O,O,N-trimethylcoclaurine (X), respectively.

By comparison of the values of the specific rotations of each of the bisected bases obtained by the cleavage reactions with the above three instances of the oxyacanthine type of bases, with those of their original bases, Tomita and Fujita[10] gave the following two interpretations concerning the steric configurations of the two asymmetric centers in the original bases: (1) The steric configuration of the right-hand center of asymmetry may have undergone inversion by the cleavage reactions; (2) each of the bisected bases may have been obtained without undergoing such inversion in the absolute configuration of the center of asymmetry in the original bases during the course of the reaction.

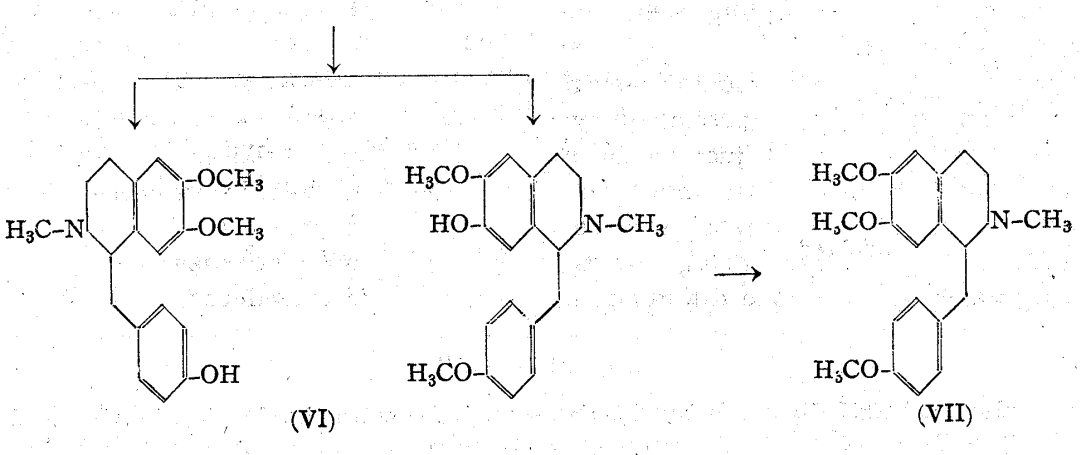
(1) If the inversion is postulated to have taken place, the steric configurations of the two asymmetric centers in the original oxyacanthine,r epandine, and cepharanthine should be (+, +), (+, −), and (+, +), respectively. (2) If the cleavage reaction is postulated to have caused no change in the absolute configurations, those of the original bases should be (+, −), (+, +), and (+, −), respectively.

From the results of the present experiments, an indirect evidence has been furnished that trilobine ($[\alpha]_D^9$: +302.8° in chloroform) and isotrilobine ($[\alpha]_D^8$: +314.8° in

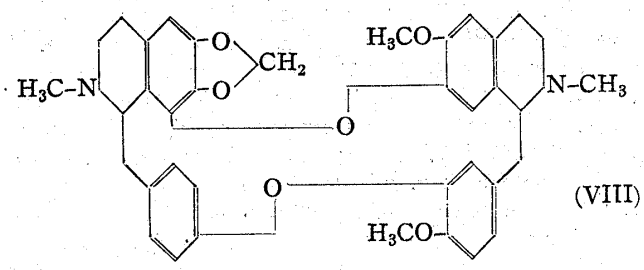
7) E. Fujita: J. Pharm. Soc. Japan, 72, 213, 217 (1952).
8) E. Fujita, T. Saijoh: *Ibid.*, 72, 1232 (1952).
9) M. Tomita, Y. Sasaki: This Bulletin, 1, 105 (1953).
10) M. Tomita, E. Fujita: *Ibid*,. 1, 101 (1953).



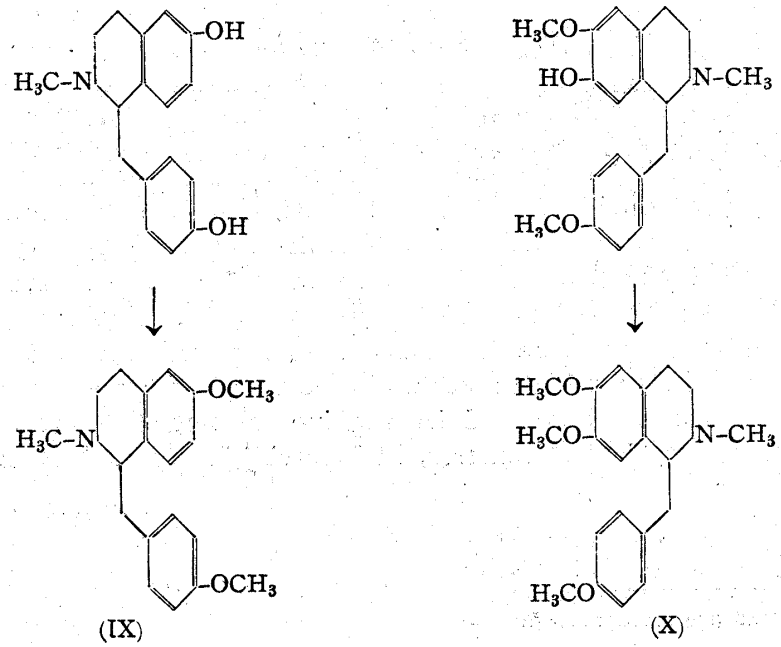
(V)



(VI) (VII)



(VIII)



(IX) (X)

chloroform) are optically isomeric with each other, both belonging to the (IV) type bases derivable from oxyacanthine, and that in spite of trilobine and isotrilobine showing the same value of $[\alpha]_D$: +300°, the two centers of asymmetry in these bases may well be assumed to be (+, −) and (−, +), or *vice versa*. This fact may serve as an additional evidence for the above view (2) that in the cleavage reaction of the oxyacanthine type of bases, such as O-methyloxyacanthine, O-methylrepandine, and cepharanthine, by metallic sodium in liquid ammonia, no Walden inversion takes place, and consequently their absolute configurations of the centers of asymmetry do not change.

On the basis of the foregoing results, it can be concluded indirectly that trilobine and isotrilobine should be optically isomeric with each other, both belonging to certain anhydro bases derivable from the oxyacanthine type of bases. The study on the anhydro-base obtained by allowing oxyacanthine to react with hydrobromic acid, is now being continued, the details of which will be published in the succeeding issues of this Bulletin.

The authors are indebted to Dr. Uno of this Institute for X-ray powder photography and to Mr. Matsui of the Shionogi Laboratory for infrared spectra. They are also indebted to the Ministry of Education for a Grant from the Scientific Research Fund.

Experimental[11]

Comparison of Trilobine Methyl Methine with Isotrilobine Methyl Methine—A portion of the specimen of trilobine methyl methine, m.p. 105~107° (efferv.), was dissolved in a small amount of alcohol, and on addition of a few drops of conc. hydrochloric acid, the hydrochloride crystallizing in needles deposited out. This was collected by filtration, dissolved in water by warming, and made alkaline by the addition of aqueous sodium hydroxide. The alkaline solution was extracted with ether, the ether extract dried with anhydrous potassium carbonate, and the solvent removed. The residue was dissolved in a small amount of benzene, and purified by passing through an alumina column (1×5 cm.). The initial eluate fraction was treated with acetone and gave needle-shaped crystals, m.p. 108~110° (efferv.). After having been dried *in vacuo* at 80° over phosphorus pentoxide for 3 hrs., they showed the m.p. of 108~114°. When the time for drying was prolonged to 2 days under the same condition, the melting point was raised to 113~115°.

Meanwhile, a portion of the specimen of isotrilobine methyl methine, m.p. 113~115°, was purified through its hydrochloride by the same procedure as described in the case of the above trilobine methyl methine, and the regenerated base showed the m.p. of 108~114° after recrystallization from acetone. Its melting point, however, was raised to 113~115° when dried *in vacuo* at 80° over phosphorus pentoxide for 2 days. A mixed m.p. of trilobine methyl methine, m.p. 113~115° with isotrilobine methyl methine, m.p. 113~115°, showed no depression.

Summary

In a series of the previous papers, it was shown that the trilobine-type bases (II (−, +,)) and (II (+, +)) were synthesized from isotetrandrine (I (−, +)) and tetrandrine (I (+, +)), belonging to the oxyacanthine-berbamine series, but these bases all agreed with neither trilobine nor isotrilobine itself, and also their methine bases were not idential with any of those of trilobine and isotrilobine. These experimental results led to a suggestion that both trilobine and isotrilobine should have the structure of (IV) type, derivable from the oxyacanthine type base (III). Thus, it became necessary to reinvestigate optically inactive trilobine methyl methine and isotrilobine methyl methine, with the results that both methine bases were confirmed to be identical. It follows, therefore, that trilobine and isotrilobine are not structurally isomeric, as so far considered, but are optically isomeric, both having the structure of (IV) type.

(Received October 29, 1953)

11) All melting points are uncorrected.