whereupon 0.57 g. of slightly yellowish crystals of m.p. 168~173° deposited. Further recrystallization from benzene or toluene yielded floral aggregates of colorless needles, m.p. 176~177°; $[\alpha]_D^{30}$: +62.8° (7.966 mg. Subst. in 1 cc. $CHCl_3$, $l$=0.5 dm.). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.10. Found: C, 72.26; H, 7.19.

(b) 2 g. of isotetrandrine dissolved in 20 cc. of toluene was cleaved by a procedure similar to that described in the previous paper[2] and the products were separated as above. The yellowish oily phenolic fraction was dissolved in a small portion of MeOH, and by allowing the solution to stand, 0.6 g. of the crude white crystals were obtained. By recrystallization from MeOH they crystallized in colorless prisms. A sample, when heated, melted at 138~140° with frothing, and upon cooling solidified, after which, when again heated, it melted at 176~177° without melting at around 140° any longer. Crystallization from abs. EtOH or benzene, however, did not afford the product of m.p. 138~140°, but of m.p. 176~177°.

**Paper Chromatography**—The paper chromatography was carried out according to the method of Kidd and Walker.[4] Toyo Roshi No. 50 paper was immersed in 0.2 *M* aq. $KH_2PO_4$, pressed between filter papers to remove excess of the liquid, dried at 100°, and allowed to equilibrate against atmospheric moisture for several hours before use. Development was effected by the descending method with the upper layer of a mixture of 63 cc. BuOH, 10 cc. AcOH, and 27 cc. of water. The Rf values for *d*-N-methylcoclaurine (m.p. 176~177°) obtained by the above fission, and for *dl*-N-methylcoclaurine[5] (m.p. 161~162°)(ca. 60 $\gamma$ used in each case) were both 0.73 using the Dragendorff reagent.

## Summary

Evidence has been presented that *d*-N-methylcoclaurine (III) forms a hemihydrate having the m.p. of 139~139.5°, and its anhydrate shows the m.p. 176~177°, quite identical with that recorded by Kidd and Walker[4] for *l*-N-methylcoclaurine, m.p. 176~177°.

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85. **Masao Tomita and Yoshio Sasaki**: Studies on the Alkaloids of Menispermaceous Plants. CXX[1]. Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia. (3)[2].

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In an earlier paper[2] of this series, it was shown that as a result of the fission of cepharanthine (I) by the sodium-liquid ammonia process, a base possessing two phenolic hydroxyl and no methoxyl groups, corresponding to *d*-1-(4′-hydroxybenzyl)-6-hydroxy-N-methlyl-1,2,3,4-tetraydroisoquinoline (II), was obtained in a crystalline form after chromatography, and on this basis formula (I) was proposed for cepharanthine. At that time, however, attempts to isolate the other phenolic fragment in crystalline form, corresponding to *l*-1-(4′-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III), were unsuccessful. Although the *l*- and *d*-forms of (III) were obtained previously from O-methyloxyacanthine[3] and O-methylrepandine,[4] respectively, by the same mode of cleavage, at that time, they were characterized as the corresponding *l*- and *d*-O,O,N-trimethylcoclaurine (IV), respectively, because of the difficulty of crystallization.

In the present series of experiments, special attention was placed on the base (III) obtainable by the cleavage of cepharanthine, and this paper deals with the isolation of this particular base (III) from the resinous phenolic fraction left after the removal of the base (II). As described in the experimental section, a product forming a crystalline

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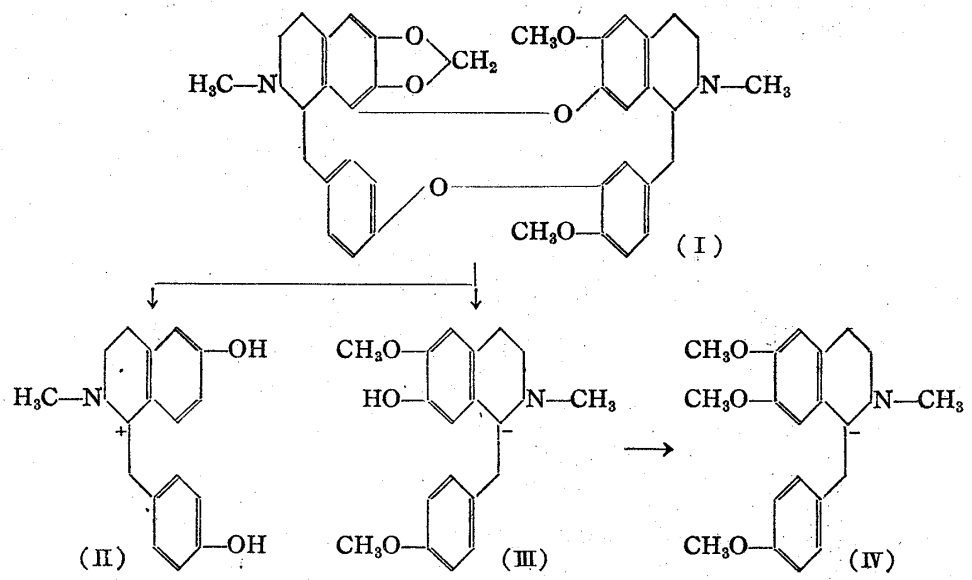
1) Part CXIX. M. Tomita, Y. Inubushi, K. Ito: This Bulletin, **2**, 372(1954).
2) Part (2). M. Tomita, Y. Sasaki: *Ibid.*, **2**, 89(1954).
3) E. Fujita: J. Pharm. Soc. Japan, **72**, 213, 217(1952).
4) E. Fujita, T. Saijoh: *Ibid.*, **72**, 1232(1952).

picrate was obtained after purification by chromatography. This substance crystallized from methanol as transparent yellow pillars melting at 100~102°, which after drying at room temperature *in vacuo* over phosphorus pentoxide, became opaque yellow pillars, m.p. 110~112°. Further drying at 70° *in vacuo* over phosphorus pentoxide for 4 days gave orange yellow needles melting at 136°, and the analytical data represented a composition of an anhydrous picrate of the base (III): The methoxyl determination revealed the presence of two methoxyl groups. This picrate was confirmed by direct comparison to be identical with that of a phenolic base obtained from epistephanine by the same mode of fission, as will be described in the succeeding paper[5] of this series. However, various attempts to crystallize the free base from this picrate failed. The specific rotation of




this noncrystallizable base was measured in methanol and showed $[\alpha]_D^{20}$: −137°. Subsequently, this was methylated with diazomethane and the resulting methyl ether was converted into the methiodide, which crystallized in colorless pillars, m.p. 136° (sintering at 128°). This methiodide agreed well in all respects with *l*-O,O,N-trimethylcoclaurine methiodide[6] (IV), and when mixed, no melting point depression was observed, thus confirming them to be identical. For the sake of confirmation, when mixed with *d*-O,O,N-trimethylcoclaurine methiodide, m.p. 136° (sintering at 128°), an evident depression of the m.p. occurred, melting at 120~125°.

From the foregoing experimental results, it is clear that the picrate, m.p. 136°, referred to above, should be identical with *l*-1-(4′-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III) picrate. Thus it has been established that the two phenolic bases obtained by the sodium-liquid ammonia fission of cepharanthine are (II) and (III), and consequently, the structure of cepharanthine must be represented by formula (I).

The authors wish to express their appreciation to Mr. M. Akasu of Kaken Chem. Drug Co. Ltd., for his generous gift of a sample of cepharanthine. The cost of this investigation was partly met by the Grant in Aid of Scientific Research from the Ministry of Education and is hereby gratefully acknowledged.

## Experimental[7]

### Treatment of Bisected Phenolic Bases

5) M. Tomita, E. Fujita: This Bulletin, **2**, 378(1954).
6) M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, **71**, 226, 1035(1951).
7) All melting points are uncorrected. The authors are indebted to Mr. K. Hozumi and his associates of the Microanalytical Laboratory of this Institute, for the microanalyses.

**Isolation of *d*-1-(4′-Hydroxybenzyl)-6-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II)**—1.8 g. of cepharanthine–benzene adduct was cleaved by a procedure similar to that described in the previous paper[2], and yielded 1.5 g. of a mixture of phenolic bisected bases. This was dissolved in the minimum amount of acetone, passed over a column of acetone-moistened Brockman's alumina (1.5×20 cm.) and the chromatogram developed with acetone. Each eluate fraction (20 cc.) was freed from the solvent, with the result shown in Table I. The crystals from the fraction Nos. 6~9, which are sparingly soluble in $CHCl_3$, were separated readily from the contaminated resinous matter, and then combined with the crystals from the fraction Nos. 10~13. The combined crystals were recrystallized from acetone and yielded 0.5 g. of (II), m.p. 205~207°(decomp.).

Table I.

| Fraction No. | | |
|---|---|---|
| 1 | Resinous oil | soluble in $CHCl_3$ |
| 2 | 〃 | |
| 3 | 〃 | |
| 4 | 〃 | |
| 5 | 〃 | |
| 6 | Crystals contaminated with resinous oil | sparingly soluble in $CHCl_3$ |
| 7 | 〃 | |
| 8 | 〃 | |
| 9 | 〃 | |
| 10 | Crystals | prisms, m.p. 205~207° (decomp.), from acetone |
| 11 | 〃 | |
| 12 | 〃 | |
| 13 | 〃 | |
| 14 | Amorphous powder | |

**Isolation of *l*-1-(4′-Methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III)**—The resinous oils left after separation of the base (II) from the fraction Nos. 1~5 and Nos. 6~9 were combined and chromatographed on Brockman's alumina (1.0×25 cm.), using $CHCl_3$ and $CHCl_3$–acetone. As the base (III) was found to show a tendency to be adsorbed in alumina column considerably tenaciously, development was continued with $CHCl_3$–acetone after development with $CHCl_3$. The product thus obtained was an oil, which did not readily crystallize, and so after removal of the solvent, it was treated with an ethanolic picric acid solution and the resulting mixture allowed to stand in an ice chest for several days, giving a crystalline picrate shown in Table II.

Table II.

| Solvent $CHCl_3$ + $Me_2CO$(Vol.) | Fraction No. | Meyer Reag. Test | Picrate, m.p., °C |
|---|---|---|---|
| 10 : 0 | 1~10(each 5 cc.) | + | 75~85 |
| 9 : 1 | 11(35 cc.) | + | 70~80 |
| 8 : 2 | 12(35 cc.) | + | 〃 |
| 7 : 3 | 13(35 cc.) | + | 〃 |
| 6 : 4 | 14~16(each 35 cc.) | + | 〃 |
| 5 : 5 | 17(35 cc.) | ± ? | |
| 4 : 6 | 18(35 cc.) | − | |

The picrate obtained was recrystallized from MeOH and formed transparent yellow pillars, m.p. 100~102°. After drying at room temperature *in vacuo* over $P_2O_5$, it became orange yellow pillars, m.p. 110~112°. Further drying at 70° *in vacuo* over $P_2O_5$ for 4 days gave orange yellow needles, m.p. 136°. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot C_6H_3O_7N_3$: C, 55.35; H, 4.79; $OCH_3$, 11.44. Found: C, 55.21; 55.34; H, 4.85, 5.26; $OCH_3$, 11.89.

30 mg. of this picrate was dissolved in acetone and passed over a column of Brockman's alumina (0.8×8 cm.), whereupon a slightly yellowish free base was obtained. Various attempts to crystallize it failed, and the specific rotation of this amorphous base was determined; $[\alpha]_D^{20}$: −137°(8 mg. in 2.9 cc. MeOH, $l$=0.25 dm.).

**Preparation of *l*-O,O,N-Trimethylcoclaurine Methiodide from *l*-1-(4′-Methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III)**—About 10 mg. of the free base from the picrate was dissolved in a small amount of MeOH and 50 cc. of an ethereal diazomethane added, after which the mixture was allowed to stand for 2 days. On removal of the excess diazomethane and the ether, a slightly yellowish oil was obtained, which was dissolved in ether and washed with 1% NaOH solution. The ethereal layer was dried over anhyd. $K_2CO_3$ and the ether removed, yielding an oil. This was refluxed with MeI in MeOH for 40 mins., after which the MeOH and the excess MeI were removed, depositing colorless pillars. Recrystallization from anhyd. EtOH showed m.p. 136°(sint. at 128°), undepressed on admixture with *l*-O,O,N-trimethylcoclaurine methiodide, m.p.

136°(sint. at 128°). A mixed m.p. with *d*-O,O,N-trimethylcoclaurine methiodide, m.p. 136°(sint. at 128°), showed a distinct depression (m.p. 120~125°, sint. at 115°).

**Identity of *l*-1-(4'-Methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III) Picrate, m.p. 136°, with Picrate, m.p. 136°, of the Bisected Base from Epistephanine** —Fujita[5] carried out the cleavage of epistephanine by the sodium-liquid ammonia process, and obtained a bisected phenolic base as a picrate crystallizing in orange yellow needles, m.p. 136°. This picrtae was confirmed by admixture to be identica with *l*-1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III) picrate, m.p. 136°. Furthermore, as a result of the paper chromatography, both gave the same Rf value as shown below :

| | Rf of the base | Rf of picric acid |
|---|---|---|
| Picrate (from epistephanine) | 0.85 | 0.66 |
| Picrate (from cepharanthine) | 0.85 | 0.66 |

Toyo Roshi No. 50 was used and development was effected by the ascending technique with the upper layer of a mixture of 67 cc. of BuOH, 27 cc. of water, and 10 cc. of glacial AcOH. For the detection of alkaloidal spots, fluorescence by the ultraviolet rays and the Dragendorff reagent were used.

## Summary

In the previous paper of this series, it was shown that the fission of cepharanthine by the sodium-liquid ammonia process gave a base possessing two phenolic hydroxyls and no methoxyl group, corresponding to (II), as crystals, and on this basis formula (I) was proposed for cepharanthine. In the present series of experiments, an attempt to isolate (III) as the picrate from the mother liquor of (II) has been successful. From these experimental results, formula (I) previously proposed by the authors for cepharanthine was confirmed.

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## 86. Masao Tomita* and Eiichi Fujita** : Studies on the Alkaloids of Menispermaceous Plants. CXXI[1]. Cleavage of Epistephanine by Metallic Sodium in Liquid Ammonia.

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Epistephanine is one of the biscoclaurine alkaloids contained in *Stephania japonica* Miers (Japanese name " Hasunoha-Kazura "), and its chemical constitution was first studied by Kondo and Tanaka[2] who proposed its structure to be one of the formulae (I)~(IV). Subsequently, Tomita and Uyeo[3], by comparative study of ultraviolet absorption spectra of miscellaneous dihydroisoquinoline derivatives, pointed out that either formula (III) or (IV) would be the most appropriate for the representation of epistephanine. Furthermore, by our recent work on the fission of isotetrandrine[4], tetrandrine[5], O-methyloxyacanthine[6], and O-methylrepandine[7] by the sodium-liquid ammonia process, the differentiation in the structure between the oxyacanthine and berbamine series, which has hitherto remained

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1) Part CXX. M. Tomita, Y. Sasaki : This Bulletin, **2**, 375(1954).
2) H. Kondo, K. Tanaka : J. Pharm. Soc. Japan, **63**, 267, 273(1943); *ibid.*, **64**, 28(1944).
3) M. Tomita, S. Uyeo, K. Doi, T. Miwa : *Ibid.*, **69**, 22(1949) (C.A., **44**, 4476(1950)).
4) M. Tomita, E. Fujita, F. Murai : *Ibid.*, **71**, 226, 1035(1951); M. Tomita, Y. Inubushi, H. Niwa: *Ibid.*, **72**, 211(1952).
5) E. Fujita, F. Murai : *Ibid.*, **71**, 1039(1951).
6) E. Fujita : *Ibid.*, **72**, 213, 217(1952).
7) E. Fujita, T. Saijoh : *Ibid.*, **72**, 1232(1952).