20. **Masao Tomita and Tohru Kikuchi**: Studies on the Alkaloids of Menispermaceous Plants. CXXIV.[1] Alkaloids of *Menispermum dauricum* DC. (Suppl. 1)

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It is now known that the rhizome of Japanese *Menispermum dauricum* DC. (Japanese name "Kohmori-kazura") contains dauricine, and the Manchurian drug "Sanzukon" (rhizome of *M. dauricum* DC.), dauricine together with a small amount of tetrandrine. The chemical structure of the tertiary base, dauricine, has already been studied and established by H. Kondo[2] and his co-workers, but the invesfigation of the quaternary bases present was left undone. We have taken it up again and this paper deals with the results thereby obtained.

By treatment with a procedure described in the experimental section two kinds of crystalline picrates were isolated. The picrate of base I was obtained as yellow needles, m.p. 201~202°, and that of base II, as yellow crystals, m.p. 199~201° (decomp.). The content of the latter picrate was far smaller than that of the former. The base I was found to be a new one, for which the name menisperine is proposed. By analyses, menisperine picrate was found to possess a formula $C_{21}H_{26}O_4N\cdot C_6H_2O_7N_3$. Menisperine gave a well-crystallizing chloride as colorless needles, m.p. 219°(decomp.), $[\alpha]_D^{24}$: +223.2° (H_2O). The analyses were in accord with the formula $C_{21}H_{26}O_4NCl$ and revealed the presence of three methoxyls and one $N(CH_3)_2$ group. It produced a brown color with ferric chloride and a brick red color with the Millon reagent. It gave a dark green color changing to blue with the Gibbs reagent. The test for a methylenedioxy group with the Gaebel reagent was negative. The infrared spectrum showed a phenolic hydroxyl absorption at 3.11 μ. The ultraviolet absorption spectrum resembles those of the aporphine alkaloids, as shown in Fig. 1.

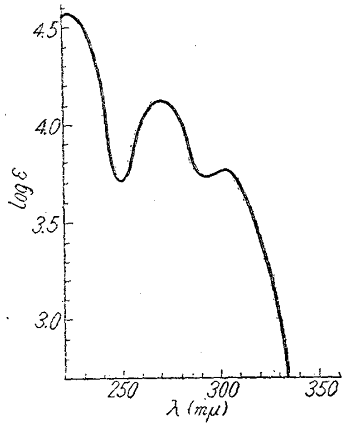

Fig. 1.

Menisperine Chloride (in H_2O)

These experimental data of menisperine suggested its relationship to the aporphine alkaloids, and thus the formula may be indicated as follows:

$$C_{21}H_{26}O_4\overset{+}{N}=C_{16}H_{10}\cdot(OCH_3)_3\cdot OH\cdot\overset{+}{N}(CH_3)_2$$

On methylation with methanolic potash and methyl iodide menisperine chloride yielded O-methylmenisperine iodide which formed colorless pillars, m.p. 244~245°(decomp.), $[\alpha]_D^{19}$: +214.6° (CH_3OH). It gave values corresponding to a composition of $C_{22}H_{28}O_4NI$

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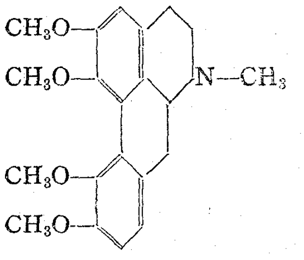
[1] Part CXXIII. M. Tomita, Y. Inubushi, E. Fujita: This Bulletin, **3**, 97(1955).

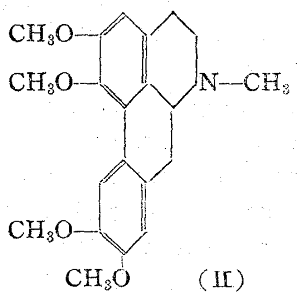
[2] M. Tomita: Fortschr. Chem. org. Naturstoffe, **9**, 192(1952); R. H. F. Manske, H. L. Holmes: "The Alkaloids," **IV**, 207(1954).

and in the methoxyl estimation, four methoxyls were confirmed.

Among the tertiary aporphine alkaloids so far recorded in the literature, possessing four methoxyl groups, (I) and (II) which differ from each other in the orientation of their methoxyl groups, are at present known.



(I)



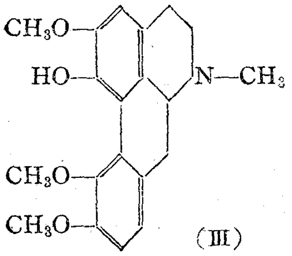
(II)

Of these, the m.p. and other data of O-methylmenisperine iodide agree closely with those of the methiodide of (I), as shown in Table I. On admixture with *d*-O,O-dimethylmagnoflorine iodide[3] (*d*-O,O-dimethylcorytuberine (I) methiodide), no depression in the m.p. was observed, and the two substances also gave identical infrared spectra, thus confirming them to be identical.

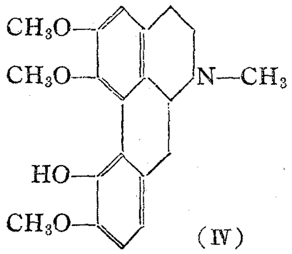
Table I.

O-Methylmenisperine iodide	m.p. 245°(decomp.)(uncorr.)	$[\alpha]_D^{19}$: +214.6°(MeOH)
O,O-Dimethylmagnoflorine iodide[3] (O,O-Dimethylcorytuberine (I) methiodide)	m.p. 244~245°(decomp.)(uncorr.)	$[\alpha]_D^{16}$: +224.2°(MeOH)
O,O-Dimethyllaurifoline iodide[4] (Glaucine (II) methiodide)	m.p. 221°	$[\alpha]_D^{16}$: +216.1°(MeOH)

For the determination of the position of one phenolic hydroxyl group in menisperine, comparison was made with the aporphine bases of type (I) possessing one phenolic hydroxyl and three methoxyl groups, of which the literature records two kinds of bases, corydine (III) and isocorydine (IV).



(III)



(IV)

On treatment with potassium iodide, menisperine was converted into the iodide crystallizing in colorless pillars, m.p. 225~226° (decomp.). Analyses gave values corresponding to a composition of $C_{21}H_{26}O_4NI$ and $[\alpha]_D^{18}$: +139.2° (CH_3OH). From these results it seemed very probable that this iodide must be identical with *d*-isocorydine methiodide[5] listed in Table II. This supposition may be also supported by the fact that menisperine gave a positive Gibbs' reaction. The identity of menisperine iodide was established by admixture with *d*-isocorydine methiodide[6] and by comparison of their infrared spectra. Thus, for the representation of menisperine, formula (V) may be considered as appropriate.

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[3] T. Nakano: This Bulletin, **2**, 329(1954).

[4] M. Tomita, F. Kusuda: This Bulletin, **1**, 5(1953).

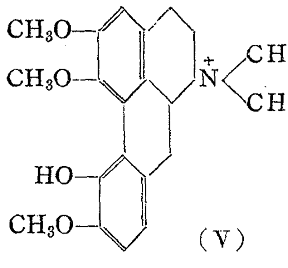
[5] E. Schlittler, H. U. Huber: Helv. Chim. Acta, **35**, 111(1952).

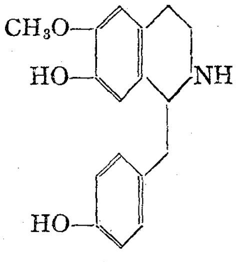
[6] This sample was supplied to us through the kindness of Dr. R. H. F. Manske. For this substance the literature records m.p. 235°(decomp.)(corr.), but as determined by us, it had m.p. 225°(decomp.) (uncorr.).

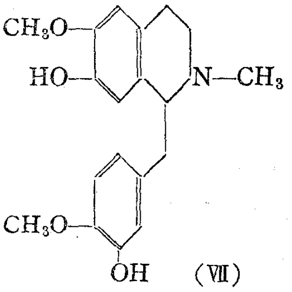
Table II.

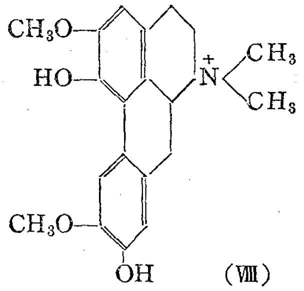
Menisperine iodide	m.p. 225~226°(decomp.)(uncorrr.)	$[\alpha]_D^{18}$: +139.2°(MeOH)
Isocorydine (IV) methiodide[6]	m.p. 225°(decomp.)(uncorrr.)	$[\alpha]_D$: +142°($CHCl_3$)
Corydine (III) methiodide	m.p. 228~230°	$[\alpha]_D$: +154°(50% EtOH)

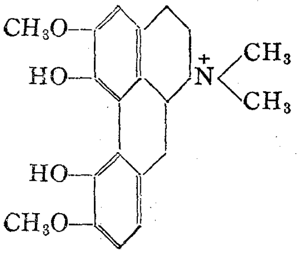
The earlier work in our laboratory showed that *Cocculus laurifolius* DC.[7] (Menispermaceae) furnished coclaurine (VI) as the secondary base, together with trilobine of the biscoclaurine type, coclanoline (VII) as the tertiary base and laurifoline (VIII) as the quaternary base. Meanwhile, more recently, it has become clear that magnoflorine (IX) occurs in *Magnolia grandiflora* L.[3] (Magnoliaceae). In this connection, it is interesting to investigate these facts from a genetic as well as biochemical standpoint. The discovery of menisperine (V), belonging to the aporphine type of quaternary bases, is the third instance following that of laurifoline (VIII) and magnoflorine (IX).


(V)


(VI)


(VII)


(VIII)


(IX)

We are indebted to Dr. R. H. F. Manske for his generous gift of a sample of *d*-isocorydine methiodide, and to Messrs. Matsui and Narisada of the Research Laboratory, Shionogi & Co., Ltd. for the measurement of infrared spectra. This work was supported by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which our thanks are due.

Experimental*

(1) **Extraction and Isolation of Alkaloids**—The undried rhizome (3.5 kg.) of *Menispermum dauricum* DC., collected in August, 1952, at Hanase district in Kyoto City, was coarsely ground and extracted 5 times with boiling MeOH. The MeOH extracts were combined and MeOH was evaporated under reduced pressure. The dark brown, sticky residue was treated several times with 3% aq. HCl. The combined acid extract was concentrated *in vacuo* to about 1 L., and filtered after cooling. The filtrate was shaken with successive portions of ether to remove acidic and neutral substances. Subsequently the aqueous phase was made alkaline by addition of sat. aq. Na_2CO_3, and the depositing basic substance was taken up in ether. The ether extract was dried over anhyd. K_2CO_3, and the ether distilled off, leaving a crude tertiary bases as yellowish brown powder (19 g.). The ether layer was treated with 5% aq. NaOH to extract the phenolic tertiary bases. NaOH solution, after acidification with HCl, was basified with Na_2CO_3 and extracted with ether. This process was repeated 6 times, and the ether extracts were combined, dried over anhyd. K_2CO_3, and the ether removed, yielding a pale yellow

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7) M. Tomita, F. Kusuda: This Bulletin, 1, 1, 6, 55, 189(1953).

* All melting points are uncorrected. We wish to express our thanks to Mr. K. Hozumi and his associates for the microanalyses.

powder. Yield, 15 g. (dauricine).

Meanwhile, Na_2CO_3-alkaline solution, free from tertiary bases by the above ether extraction, was immediatelty made acid to Congo red paper with 30% H_2SO_4, and treated with 0.5 *N* basic lead acetate (about 500 cc.). The resulting precipitate was removed, and the excess lead acetate was decomposed with H_2S. The filtered solution was concentrated to 1 L. under a reduced pressure and neutralized with aq. NaOH. Then, 50% H_2SO_4 was added so that the solution was kept at the acidity of 5% H_2SO_4, after which the solution was treated with 25% phosphotungstic acid solution in 5% H_2SO_4 until no further precipitation was obtained. After standing overnight to ensure complete precipitation, the precipitate was filtered, suspended in a small portion of acetone, and decomposed with hot sat. $Ba(OH)_2$ solution in excess. The alkaline filtrate from the barium phosphotungstate was neutralized exactly to Congo red with 50% H_2SO_4, $BaSO_4$ was removed, and the filtrate subjected to exact double decomposition with aq. $BaCl_2$. The filtrate now containing chlorides of quaternary bases, was concentrated *in vacuo* to approx. 300 cc., the pH of the solution was adjusted to 6~7 (bromocresol purple or bromothymol blue) with 10% NaOH, and the resulting solution was saturated with finely powdered $HgCl_2$. $HgCl_2$ salt of quaternary bases precipitated as a dark brown paste (40 g.), which was collected, suspended in MeOH, and decomposed by H_2S. The filtrate from HgS was evaporated to dryness *in vacuo*, yielding a dark brown powder (26 g.) of quaternary bases. After two more repetition of $HgCl_2$ process, $HgCl_2$ salts became a slightly brownish powder, from which quaternary base chlorides were obatined as an amorphous powder (15 g.). All attempts to induce this powder to crystallize failed. The powder (13 g.) was dissolved in water and an aq. ammonium reineckate saturated below 60° was added until the supernatant solution no longer showed any turbidity with an additional reagent, and after standing overnight, the rose-colored muddy precipitate was collected, kept in air, and dried in a desiccator *in vacuo*; the crimson powder (20 g.) was chromatographed in acetone on alumina. A column (3×25 cm.) containing Brockmann's alumina wetted with dry acetone was prepared, the solution of the reineckates (20 g.) in dry acetone (70 cc.) was run through, and the column developed with acetone. The filtrate was divided into 4 fractions, each being crimson-colored.

Fraction I. The solution (150 cc.) was treated with hot sat. aq. Ag_2SO_4 until no further precipitation of silver reineckate occurred. After cooling, the precipitate was filtered off and washed thoroughly with water. The filtrate and washings were combined and aq. $BaCl_2$ was added to convert the quaternary base sulfates into the chlroides and to precipitate any excess Ag_2SO_4. The filtrate from AgCl and $BaSO_4$ was evaporated *in vacuo* to dryness, leaving a slightly brownish powder. This was dissolved in a small quantity of EtOH, insoluble inorganic substances were removed, and the filtrate was concentrated, leaving a pale brownish syrupy residue which could not be crystallized. The residue was dissolved in water and cold sat. aq. Na picrate added. The resulting yellow precipitate was collected and treated with acetone, depositing crystals. Upon recrystallization from acetone-MeOH, yellow needles, m.p. 201~202°, were obtained (base I picrate). Yield, 1.6 g.

Fraction II. The fraction (200 cc.) was treated in the same manner as fraction I, and likewise converted into the picrates. However, the major part of the picrates gave a yellow brown syrup, from which only a trace of crystals were obtained, too small to permit further work.

Fraction III. From this fraction (350 cc.), a small quantity of yellow crystalline picrate was obtained, but the mother liquor remained a yellow syrup. Recrystallization from acetone vielded yellow needles, m.p. 199~201° (decomp.); yield, 0.02 g. (base II picrate). Admixture with base I picrate from fraction I gave a depression in m.p. (182~186°).

Fraction IV. This fraction (150 cc.) gave no crystalline picrates.

Menisperine picrate (Base I Picrate)—This picrate was readily soluble in acetone, soluble in MeOH and EtOH. It was obtained as yellow needles, m.p. 201~202°, from a mixture of acetone and MeOH. *Anal.* Calcd. for $C_{27}H_{28}O_{11}N_4$: C, 55.68; H, 4.82; N, 9.58; OCH_3, 15.92. Found: C, 55.68, 55.82; H, 4.59, 4.89; N, 9.52, 9.25; OCH_3, 16.17, 16.09.

Base II Picrate—This picrate was less soluble in acetone than menisperine picrate. It formed yellow needles, m.p. 199~201° (decomp.). Found: C, 47.98, 47.85; H, 5.24, 5.17; N, 13.43, 13.69.

(2) **Menisperine Chloride**—1.5 g. of menisperine picrate was dissolved in a small portion of acetone, treated with dil. HCl and the resulting solution was extracted with ether until all of the picric acid was removed. The nearly colorless aqueous solution was evaporated *in vacuo* to dryness, leaving a slightly brownish residue. This was dissolved in the minimum amount of MeOH, and on addition of a few drops of acetone, a greenish color resulted. Upon scratching the wall of the vessel with a glass rod colorless needles were obtained. They were readily soluble in water, MeOH, and EtOH, and insoluble in acetone. After recrystallization from MeOH-acetone, they showed m.p. 219° (decomp.). $[\alpha]_D^{24}$: +223.2° (8.960 mg. in 4 cc. of water, $l=0.3$ dm.). Yield, 0.75 g. This substance gave a brown color with $FeCl_3$ and a brick red color with conc. H_2SO_4 and $NaNO_3$. With Millon reagent it produced a brick red color, changing to pale yellowish brown on standing. With the Gibbs reagent, it developed a dark green color, which on standing for a while, varied from blue through dark blue to dark violet. The test for a methylenedioxy group with the Gaebel reagent was negative. The ultraviolet

absorption spectrum (in water) (Fig. I) : λ_{max} 303 mμ (log ε=3.76), λ_{min} 295 mμ (log ε=3.73), λ_{max} 270 mμ (log ε=4.13), λ_{min} 250 mμ (log ε=3.71). *Anal.* Calcd. for $C_{21}H_{26}O_4NCl$: C, 64.34; H, 6.74; N, 3.58; OCH_3, 23.76; $N(CH_3)_2$, 7.67. Found : C, 63.63, 63.78; H, 6.97, 7.02; N, 3.35, 3.55; OCH_3, 23.51, 23.58; $N(CH_3)_2$, 6.93.

(3) **O-Methylmenisperine Iodide**—One g. of menisperine chloride was dissolved in 3 cc. MeOH, 6 cc. of 0.5 *N* MeOH-KOH and 1.5 cc. of MeI were added, and the solution was refluxed for 2.5 hrs. After standing overnight, the solution deposited colorless crystals which were dissolved in 3 cc. MeOH with warming. The resulting solution was treated with 5 cc. MeOH-KOH and 1.5 cc. MeI, and heated gently for 4 hrs. After repetition of two such similar procedures, the solution was concentrated and deposited colorless pillars on standing. Recrystallization was effected from MeOH-H_2O, m.p. 245° (decomp.); $[\alpha]_D^{19}$: +214.6° (2.888 mg. in 1 cc. MeOH, l=0.5 dm.). Yield, 1.0 g. *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.14; H, 5.67; OCH_3, 24.95. Found : C, 53.20, 53.49; H, 5.76, 6.04; OCH_3, 23.00. A mixed m.p. with O,O-dimethylcorytuberine methiodide, m.p. 244~245° (decomp.), showed no depression. Also the infrared spectra of both substances were quite identical.

(4) **Menisperine Iodide**—0.05 g. of menisperine chloride was dissolved in the minimum amount of water and treated with KI. By scratching the wall of the vessel with a glass rod, colorless pillars separated out. They were comparatively sparingly soluble in water and MeOH. After recrystallization from MeOH-water, they showed m.p. 215° (decomp.), and after drying for 10 hrs. at 100° *in vacuo* over P_2O_5, m.p. 225~226° (decomp.). Yield, ca. 0.04 g. $[\alpha]_D^{18}$: +139.2° (4.172 mg. in 1 cc. MeOH, l=0.5 dm.). *Anal.* Calcd. for $C_{21}H_{26}O_4NI$: C, 52.16; H, 5.42; OCH_3, 19.18. Found : C, 52.51, 52.23; H, 5.54, 5.33; OCH_3, 18.66. On admixture with *d*-isocorydine methiodide, m.p. 225° (decomp.) (uncorr.), no m.p. depression was observed, and the two substances also gave identical infrared spectra.

(**Addendum**) After this paper was submitted for publication, it came to the notice of the authors that N-methylisocorydine, a quarternary alkaloid, had been isolated from the bark of *Fagara coco* (Gill) Engl. (family, Rutaceae) by J. Comin and V. Deulofeu (cf. J. Org. Chem., **19**, 1774 (1954)), from the bark of *Xanthoxylum* spp. (family, Rutaceae) by J. R. Cannon, *et al.* (cf. Australian J. Chem., **6**, 86 (1953)), and from the bark of *Legnephora Moarei* F. Muell (family, Menispermaceae) by G.K.Hughes, *et al.* (*ibid.*, **6**, 90 (1953)).

Summary

The tertiary base, dauricine, of *Menispermum dauricum* DC. had already been studied in detail and its chemical structure established, but the investigation of the quaternary bases present had been left undone. In this paper, the isolation of two quaternary bases from the same plant is presented. One of these bases, which occurs in comparatively larger amounts, was named menisperine. It was found that menisperine iodide is identical with *d*-isocorydine methiodide. For the representation of menisperine formula (V) of the aporphine type may be considered as appropriate.

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