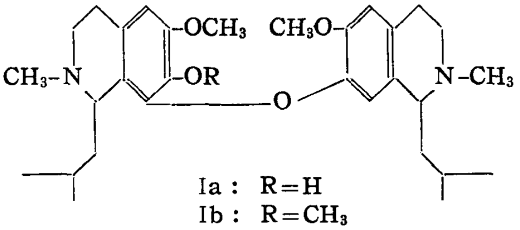
[Chem. Pharm. Bull. 11 (12) 1504 ~ 1507]

UDC 547.94 : 582.852

# 232. **Kiyoshi Bessho**[*1,*2] : Studies on Pilocereine and Related Compounds. VII.[*3] Cleavage of O-Methylpilocereine by Metallic Potassium in Liquid Ammonia.

*(Faculty of Pharmaceutical Sciences, Kyoto University*[*1])

As the result of the synthesis of O-methylisopilocereine (Ib),[*3] it was suggested that representation of O-methylpilocereine by the same formula (Ib) is untenable and reexamination of structure of the latter was required.



Ia : R=H
Ib : R=$CH_3$

The formulation of pilocereine as Ia was based on its molecular formula $C_{30}H_{44}O_4$-$N_2$[1,2] and the result of potassium-liq. ammonia cleavage reaction of its O-methyl ether (Chart 1). In this experiment, however, the bisected phenolic bases were characterized after O-methylation and therefore the locations of their phenolic hydroxyl groups remained to be confirmed. In addition, the most remarkable feature of this result was that the positions of cleavage seemed to be inconsistent with an empirical rule[3]

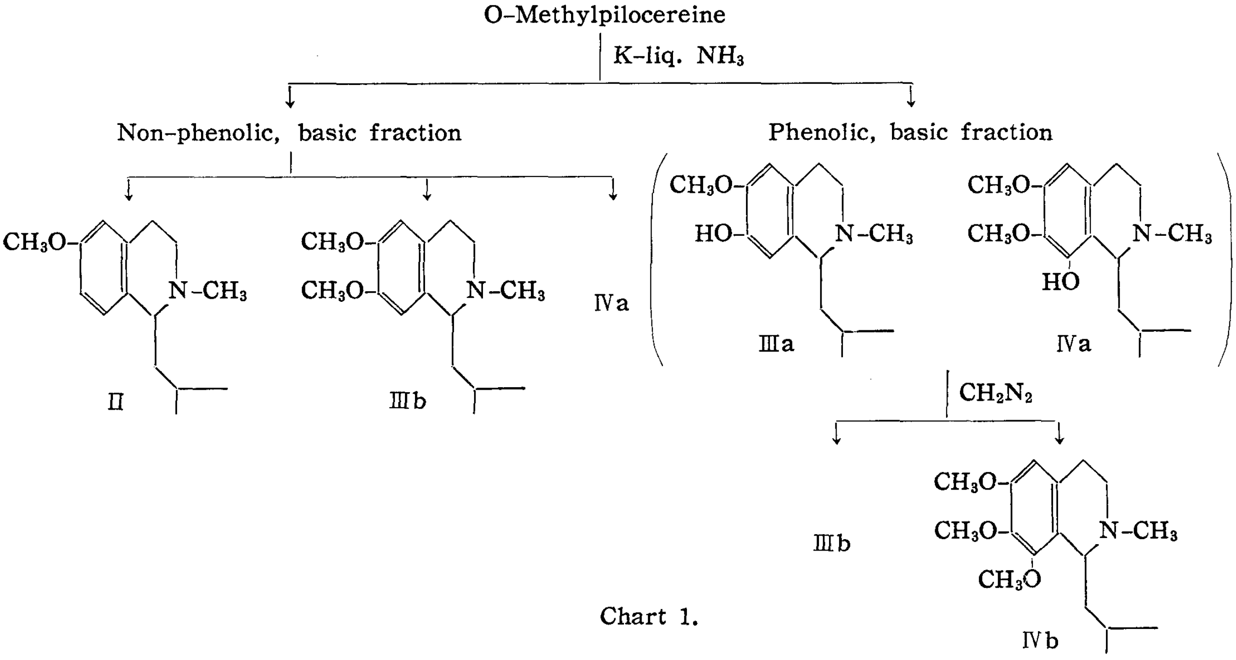


Chart 1.

---

[*1] Yoshida-konoe-cho, Sakyo-ku, Kyoto (別所 清).

[*2] Present address : Institute for Chemical Research, Kyoto University, Takatsuki-shi, Osaka.

[*3] Part VI. This Bulletin, **11**, 1500 (1963).

1) C. Djerassi, N. Frick, L.E. Geller : J. Am. Chem. Soc., **75**, 3632 (1953).

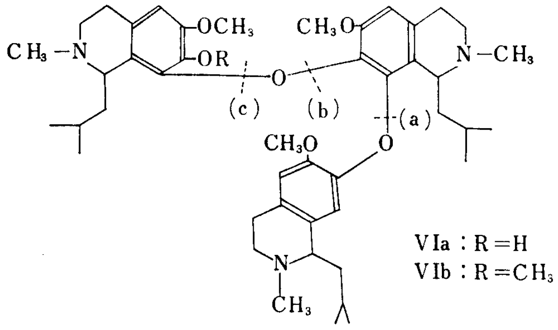
2) C. Djerassi, S.K. Figdor, J.M. Bobbitt, F.X. Markley : *Ibid.* **79**, 2203 (1957).

3) M. Tomita : Fortsch. Chem. Org. Naturstoffe, **9**, 175 (1952).

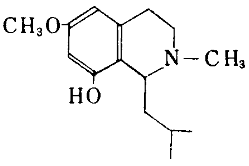
which had been deduced from the results of a number of cleavage reactions of analogous biscoclaurine alkaloids performed in our laboratory, *i.e.*, the rule predicted that a base having the structure (Ib) would be bisected to give IIIb and IIIa exclusively, and it had been proved just to be the case with O-methylisopilocereine. In order to resolve these problems, reinvestigation of this potassium-liq. ammonia procedure was attempted.

When O-methylpilocereine, m.p. 154~154.5°, was submitted to the cleavage reaction according to Djerassi's description, there were obtained nearly equal amounts of phenolic product and non-phenolic product. Separation of the phenolic bases as described in experimental part afforded lophocerine (IIIa) and 8-hydroxy-6,7-dimethoxy compound (IVa) accompanied by a small amount of a base $C_{15}H_{23}O_2N$, m.p. 130~131.° The last compound was considered to be V on the basis of the analytical data and the positive Gibbs reaction, but characterization of its O-methyl ether could not be achieved because of its poor quantity. The non-phenolic, basic fraction of the bisected product was chromatographed on alumina and there was obtained a small amount of isopilocereine (identified as the dipicrate, m.p. 234~235°) in addition to II, IIIb and a trace of the phenolic base (m.p. 130~131°) above mentioned. The formation of isopilocereine*4 and a new phenolic base (considered to be V) can not be explained with the formula (Ib).

Recently Djerassi and co-workers found that the molecular weight of O-methylpilocereine is not 510 (calcd. for Ib) but 757 by mass spectrometry and gave a revised molecular formula $C_{45}H_{65}O_6N_3$ to pilocereine. They also repeated the potassium-liq. ammonia cleavage of O-ethylpilocereine. In addition to the products reported earlier,[2)]



VIa : R=H
VIb : R=CH₃



V

there was obtained V, which afforded the known 6,8-dimethoxy compound on O-methylation. On the basis of structures of these bisected bases and of isopilocereine (Ia), structure (VIa) was proposed for pilocereine. The observation described above that a small amount of isopilocereine was found in the cleaved products of O-methylpilocereine also pointed out the same structure (VIa) for pilocereine. In view of this new formula, the formation of isopilocereine on the treatment of pilocereine with potassium-liq. ammonia can be consistently explained in accordance with Tomita's empirical rule,[3)] *i.e.*, of two diphenyl ether linkages of pilocereine, one which locates at the *o*-position of the phenolic hydroxyl group remained uneffected and the other was cleaved at (a), whose *p*-position has no substituent, to yield lophocerine (IIIa) and isopilocereine (Ia). The unexpected cleavage at the (b)-position of O-methylpilocereine (VIb) may be illustrated as the effect of an additional *o*-phenoxyl group which is absent in Ib and biscoclaurine alkaloids. On the other hand, cleavage at the (c)-position gave isopilocereine (Ia) which would remain without further fission.

---

[*4] The suspicion that this isopilocereine might originated in pilocereine which had been contaminated the starting material was eliminated since O-methylpilocereine used in this reaction did not exhibited any absorption at 3500 cm$^{-1}$ region in the infrared spectrum even when measured at high concentration.

4) C. Djerassi, H.W. Brewer, C. Clarke, L.J. Durham : J. Am. Chem. Soc., 84, 3210 (1962).

In consequence, it was proved that isopilocereine is not an anomalous rearrangement product but is one of the normal cleavage products of pilocereine and the structure (Ia), which had been inadequately assigned to pilocereine and piloceredine, could be assigned to isopilocereine without any question.

## Experimental[*5]

**O-Methylpilocereine**——A methanolic solution of pilocereine (1.10 g.) was treated with an ethereal solution of diazomethane which had been prepared from 16 g. of nitrosomethylurea. After 1 week, the same quantity of diazomethane was added and the mixture was allowed to react for additional 1 week. Usual treatment of the product yielded 1.14 g. of a non-phenolic base, which melted at 95~100° and resolidified to melt again at 153~154°. Chromatography on $Al_2O_3$ (1×15 cm.) with benzene and recrystallization from hexane gave 0.99 g. of colorless pillars, m.p. 154~154.5° (rec.1) m.p. 92~105° and 153~155°).

**Cleavage of O-Methylpilocereine by Potassium in Liquid Ammonia. i) Cleavage Reaction**——An ethereal solution of 900 mg. of O-methylpilocereine (30 ml.) was added to 300 ml. of liq. $NH_3$ and allowed to react with 900 mg. of K at −60~−58° for 7 hr. After addition of $NH_4Cl$ and evaporation of the solvent, the residue was fractionated in the usual manner to yield 440 mg. of non-phenolic, basic and 470mg. of phenolic, basic fraction.

**ii) Separation of Bisected Phenolic Bases**——Addition of 120 mg. of oxalic acid to a $Me_2CO$ solution of the phenolic, basic fraction yielded 310 mg. of the crude oxalate melting at 205~207° (decomp.), which, on repeated fractional recrystallizations from EtOH, was separated into difficultly soluble crystals and more soluble ones. Recrystallization of the former afforded 48 mg. of colorless pillars, m.p. 225° (decomp.). *Anal.* Calcd. for $C_{15}H_{23}O_2N \cdot \frac{1}{2}(COOH)_2$ : C, 65.28; H, 8.22. Found : C, 64.80, 64.69; H, 8.07, 8.10.

This compound showed light-blue color when treated with Gibbs reagent. The free base obtained from this oxalate crystallized on treatment with hexane and was recrystallized from the same solvent to yield 20 mg. of colorless octahedrons, m.p. 130~131° (probably V). *Anal.* Calcd. for $C_{15}H_{23}O_2N$ : C, 72.25; H, 9.30. Found : C, 72.08; H, 9.40.

On the other hand, the more soluble oxalate was recrystallized from EtOH to give 85 mg. of colorless pillars, m.p. 213~214° (decomp.). This compound gave negative Gibbs reaction and was identified with lophocerine (IIIa) oxalate. *Anal.* Calcd. for $C_{15}H_{23}O_2N \cdot \frac{1}{2}(COOH)_2$ : C, 65.28; H, 8.22. Found : C, 65.46; H, 8.37.

The picrate was prepared from a portion of the oxalate and obtaind as yellow, rhombic plates, m.p. 194~195°, which were identified with lophocerine (IIIa) picrate by mixed melting point and IR comparison (in Nujol). *Anal.* Calcd. for $C_{15}H_{23}O_2N \cdot C_6H_3O_7N_3$ : C, 52.71; H, 5.48. Found : C, 52.93; H, 5.76.

The mother liquors of recrystallizations of the crude oxalate were converted into the free base (97 mg.) and treated with an ethereal solution of diazoethane. The picrate of the non-phenolic product was recrystallized from EtOH to yield 130 mg. of yellow plates, m.p. 149~150° which were identified with O-ethyllophocerine picrate by mixed melting point and IR comparison (in Nujol). *Anal.* Calcd. for $C_{17}H_{27}O_2N \cdot C_6H_3O_7N_3$ : C, 54.54; H, 5.95. Found : C, 54.82; H, 6.10.

The mother liquor of the preparation of the crude oxalate was also converted into the free base and chromatographed on $Al_2O_3$[*6] (0.8×8 cm.). Elution with benzene and with benzene-$Et_2O$ (1:1) afforded an oily base which, on treatment with picric acid, gave 30 mg. of 8-hydroxy-6,7-dimethoxy compound (IVa) picrate as yellow pillars, m.p. 145~147°. *Anal.* Calcd. for $C_{16}H_{25}O_3N \cdot C_6H_3O_7N_3$ : C, 51.96; H, 5.55. Found : C, 51.93; H, 5.51.

The mother liquor of this picrate was again converted into the free base and treated with an ethreal solution of diazoethane. The non-phenolic product was sublimated at 65° (0.06 mm. Hg) yielding 10 mg. of colorless needles, m.p. 68~71°, which were considered to be 8-ethoxy-6,7-dimethoxy compound. *Anal.* Calcd. for $C_{18}H_{29}O_3N$ : C, 70.32; H, 9.51. Found : C, 69.65, 69.95; H, 9.64, 9.43.

**iii) Separation of Bisected Non-phenolic Bases**——The non-phenolic, basic fraction was chromatographed on $Al_2O_3$[*7] (1×20 cm.). Fract. 1~10 (eluted with hexane) gave 152 mg. of 6-methoxy compound (II) which was characterized as the picrate, yellow plates, m.p. 154~155°, 290 mg. *Anal.* Calcd. for $C_{15}H_{23}ON \cdot C_6H_3O_7N_3$ : C, 54.54; H, 5.67. Found : C, 54.75; H, 5.86.

---

[*5] All melting points are uncorrected.

[*6] Aluminium oxide neutral (Woelm).

[*7] Aluminium Oxide according to Brockmann (Merck), previously treated with 3 ml./100 g. of 10% AcOH.

Fractions 11~17 (eluted with hexane and with hexane-benzene (2:1)) yielded 90 mg. of O-methyllophocerine (IIIb). The picrate was recrystallized from EtOH to give 145 mg. of yellow plates, m.p. 184~185°. *Anal.* Calcd. for $C_{16}H_{25}O_2N \cdot C_6H_3O_7N_3$ : C, 53.65; H, 5.73. Found : C, 53.71; H, 5.92.

From the following hexane-benzene eluate (Fract. 19~22), 15 mg. of unchanged O-methylpilocereine was recovered as colorless pillars, m.p. 152~153° (100° sinter), and identified by mixed melting point and IR comparison (in $CHCl_3$). Fract. 23~25 (eluted with benzene and with benzene-$Et_2O$ (4:1)) yielded 30 mg. of a base. Two recrystallizations from hexane gave 15 mg. of colorless octahedrons, m.p. 130~131°. This compound showed blue color on treatment with Gibbs reagent and did not depress the melting point on admixture with the bisected phenolic base, m.p. 130~131° (see above). Fract. 27~34 (eluted with benzene-$Et_2O$ (4:1~1:1) and with $Et_2O$) was converted into the picrate and recrystallized from $Me_2CO$-EtOH to yield 38 mg. of yellow plates, m.p. 234~235°. This picrate was identified with isopilocereine dipicrate by mixed melting point and IR comparison (in Nujol). *Anal.* Calcd. for $C_{30}H_{44}O_4N_2 \cdot 2C_6H_3O_7N_3$ : C, 52.82; H, 5.28. Found : C, 52.64; H, 5.52.

## Summary

The potassium-liq. ammonia cleavage of O-methylpilocereine was carried out in order to re-examine the structure (Ia) of pilocereine. In addition to the expected bases (II, IIIb, IVa, and IIIa), isopilocereine (Ia) and a phenolic base which is considered to be V were obtained. This result and new molecular formula $C_{45}H_{65}O_6N_3$ proposed lately by Djerassi, *et al.* pointed out the structure of pilocereine to be VIa. The formation of isopilocereine on treatment of pilocereine with potassium-liq. ammonia was illustrated as a normal cleavage reaction.

(Received June 25, 1963)

---

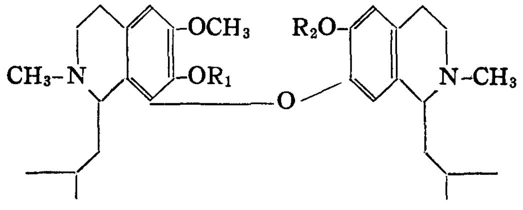
[Chem. Pharm. Bull. 11 (12) 1507 ~ 1510]

UDC 547.94 : 582.852

## 233. Kiyoshi Bessho[*1,*2] : Studies on Pilocereine and Related Compounds. VIII.[*3] Structures of Isopilocereine and Desmethylisopilocereine.

(*Faculty of Pharmaceutical Sciences, Kyoto University*[*1])

In the preceding papers, the structure of O-methylisopilocereine (Ia) was confirmed by potassium-liq. ammonia cleavage reaction and synthesis. This paper deals with the locations of the phenolic hydroxyl groups of isopilocereine and desmethylisopilocereine.



Ia : $R_1=R_2=CH_3$
Ib : $R_1=H$, $R_2=CH_3$
Ic : $R_1=R_2=H$
Id : $R_1=C_2H_5$, $R_2=CH_3$
Ie : $R_1=R_2=C_2H_5$

---

[*1] Yoshida-konoe-cho, Sakyo-ku, Kyoto (別所 清).
[*2] Present address : Institute for Chemical Research, Kyoto University, Takatsuki-shi, Osaka.
[*3] Part VII. This Bulletin, 11, 1504 (1963).