
(Faculty of Pharmaceutical Sciences, Kyoto University*3)

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 re-examination of structure of the latter was required.

The formulation of pilocereine as Ia was based on its molecular formula C_{29}H_{44}O_{4}\cdot N_{2}\cdot H_{2}O*1,*3 and the result of potassium-liquid 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

---

*1 Yoshida-konoe-cho, Sakyo-ku, Kyoto (御所 清).
*2 Present address: Institute for Chemical Research, Kyoto University, Takatsuki-shi, Osaka.
*3 Part VI. This Bulletin, 11, 1500 (1963).
which had been deduced from the results of a number of cleavage reactions of analogous bisococlaurine 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-liqu. 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 lophocereine (IIIa) and 8-hydroxy-6,7-dimethoxy compound (IVa) accompanied by a small amount of a base C_{12}H_{11}O_{2}N, 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" 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 (calc. for Ib) but 757 by mass spectrometry and gave a revised molecular formula C_{46}H_{44}O_{2}N_{3} to pilocereine. They also repeated the potassium-liqu. ammonia cleavage of O-ethylpilocereine. In addition to the products reported earlier,5)
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**

O-Methylpilocereine—A methanolic solution of pilocereine (1.10 g.) was treated with an ethereal solution of diazomethane which had been prepared from 18 g. of nitrosoethylurea. 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°C and redissolved to melt again at 153~154°C. Chromatography on Al₂O₃ (1 x 15 cm.) with benzene and recrystallization from hexane gave 0.99 g. of colorless pillars, m.p. 154~154.5°C (rec.¹) m.p. 92~105°C and 153~155°C.

**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. NH₃ and allowed to react with 900 mg. of K at -60~58°C for 7 hr. After addition of NH₄Cl 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 Me₂CO solution of the phenolic, basic fraction yielded 310 mg. of the crude oxalate melting at 205~207°C (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°C (decomp.). *Anal. Calcd. for C₁₃H₁₉O₂N·½(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°C (probably V). *Anal. Calcd. for C₁₃H₂₅O₂N: 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°C (decomp.). This compound gave negative Gibbs reaction and was identified with lophocereine (**IIIa**) oxalate. *Anal. Calcd. for C₁₃H₁₉O₂N·½(COOH)*₂: C, 65.28; H, 8.22. Found: C, 65.46; H, 8.37.

The pircate was prepared from a portion of the oxalate and obtained as yellow, rhombic plates, m.p. 194~195°C, which were identified with lophocereine (**IIIa**) pircate by mixed melting point and IR comparison (in Nujol). *Anal. Calcd. for C₁₃H₁₉O₂N·C₁₂H₂₅O₂N₂: 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 diazethane. The picrate of the non-phenolic product was recrystallized from EtOH to yield 130 mg. of yellow plates, m.p. 149~150°C which were identified with O-ethyllophocereine pircate by mixed melting point and IR comparison (in Nujol). *Anal. Calcd. for C₁₃H₁₉O₂N·C₁₂H₂₅O₂N₂: 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 Al₂O₃-**(2.8 x 1 cm.)**. Elution with benzene and with benzene–Et₂O (1:1) afforded an oily base which, on treatment with picric acid, gave 30 mg. of 8-hydroxy-6,7-dimethoxy compound (IVa) pircate as yellow pillars, m.p. 145~147°C. *Anal. Calcd. for C₁₃H₁₉O₂N·C₁₂H₂₅O₂N₂: C, 51.96; H, 5.55. Found: C, 51.93; H, 5.51.*

The mother liquor of this pircate was again converted into the free base and treated with an ethereal solution of diazoethane. The non-phenolic product was sublimated at 65°C (0.06 mm. Hg) yielding 10 mg. of colorless needles, m.p. 68~71°C, which were considered to be 8-ethoxy-6,7-dimethoxy compound. *Anal. Calcd. for C₁₃H₁₉O₂N: 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 Al₂O₃-**(1 x 20 cm.)**. Fract. 1~10 (eluted with hexane) gave 152 mg. of 6-methoxy compound (II) which was characterized as the pircate, yellow plates, m.p. 154~155°C, 290 mg. *Anal. Calcd. for C₁₃H₂₅O₂N·C₁₂H₂₅O₂N₂: C, 54.54; H, 5.67. Found: C, 54.75; H, 5.86.*

** All melting points are uncorrected.
** Aluminium oxide neutral (Woelm).
* 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-methyl-lophocerine (IIb). The picrate was recrystallized from EtOH to give 145 mg. of yellow plates, m.p. 184~185°. Anal. Calcd. for C₁₅H₁₂O₆N₃: 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-methyl pilocerine was recovered as colorless pillars, m.p. 152~153° (100° sinter), and identified by mixed melting point and IR comparison (in CHCl₃). Fract. 23~25 (eluted with benzene and with benzene-Et₂O (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 Gibbes 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-Et₂O (4:1~1:1) and with Et₂O) was converted into the picrate and recrystallized from Me₂CO-EtOH to yield 38 mg. of yellow plates, m.p. 234~235°. This picrate was identified with isopilocerine dipicrate by mixed melting point and IR comparison (in Nujol). Anal. Calcd. for C₂₅H₂₄O₄N₂·2C₂H₅O₂N₂: C, 52.82; H, 5.28. Found: C, 52.64; H, 5.52.

Summary

The potassium-liq. ammonia cleavage of O-methyl pilocerine was carried out in order to re-examine the structure (Ia) of pilocerine. In addition to the expected bases (II, IIIb, IVa, and IIIa), isopilocerine (Ia) and a phenolic base which is considered to be V were obtained. This result and new molecular formula C₁₅H₁₂O₆N₃, proposed lately by Djerassi, et al. pointed out the structure of pilocereine to be VIa. The formation of isopilocerine 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


(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.

\[
\begin{align*}
\text{Ia} & : R₁=R₂=CH₃ & \quad \text{Id} & : R₁=C₂H₅, R₂=CH₃ \\
\text{lb} & : R₁=H, R₂=CH₃ & \quad \text{le} & : R₁=R₂=C₂H₅ \\
\end{align*}
\]

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