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229. Kiyoshi Bessho[1],[2] : Studies on Pilocereine and Related Compounds. IV.[3] Synthesis of O-Methylisopilocereine. (1).

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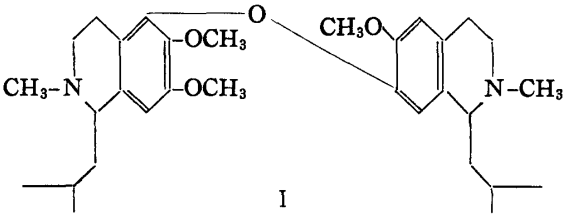
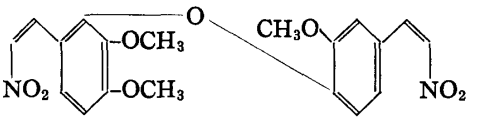
In order to synthesize I, which was supposed to be O-methylisopilocereine, an important intermediate (II) was prepared.[3] However, the poor yield of II showed that this synthetic route was unpractical. The present papar deals with the synthesis of I according to an alternative route, *i.e.* an Ullmann condensation between two kinds of isoquinoline bases.



I



II

1-Isobutyl-2-methyl-5-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII) was synthesized as shown in Chart 1, and was characterized as an oxalate, m.p. 164~165° (decomp.), and a picrate, m.p. 172~174°. Condensation of this compound with lophocerine (IX) was carried out in pyridine solution in the presence of potassium carbonate, potassium iodide, and copper powder. After removal of residual starting materials and the debrominated compound (X) by vacuum distillation, an oily base was obtained. This product showed a single spot on PPC, MPC, and PEP, but two spots were seen on

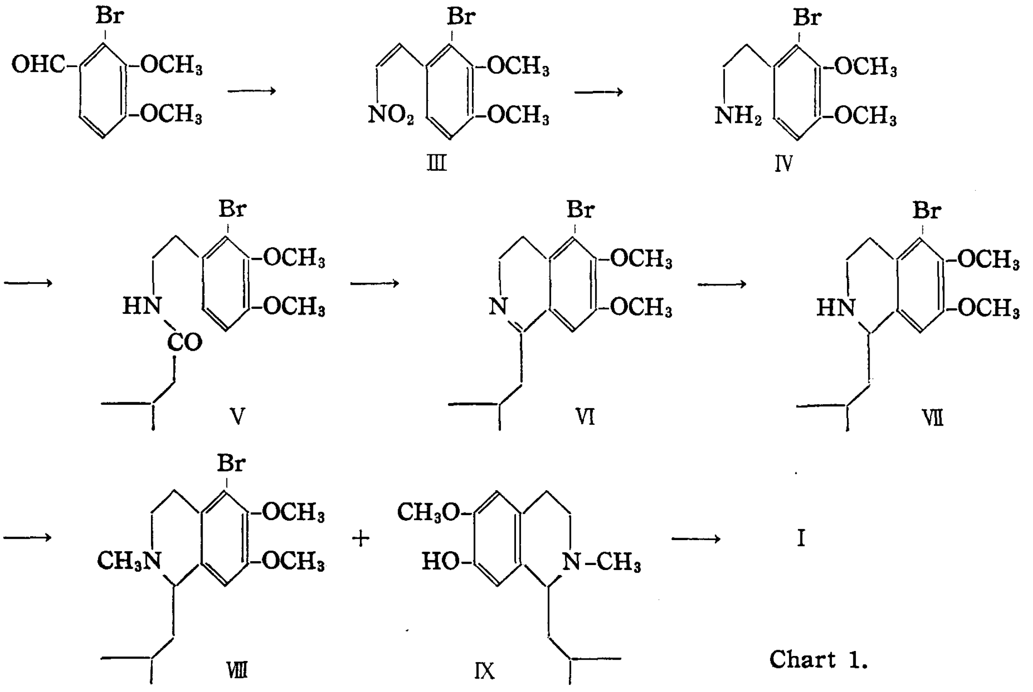


Chart 1.

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[3] Part III. This Bulletin, **11**, 1484 (1963).

TLC.*4 Repeated alumina chromatography resulted in the separation of two bases (I-A and I-B) corresponding to the two spots on TLC. These bases had identical ultraviolet spectra and their infrared spectra were also substantially the same (Fig. 1). These materials were considered to correspond to the two racemic diastereomers of I.

Although both bases of I coincided well with O-methylisopilocereine on PPC, MPC, and PEP, and also in regard to their ultraviolet spectra, several discrepancies were observed in their infrared spectra in chloroform solutions. This indicated that I was not identical with O-methylisopilocereine.

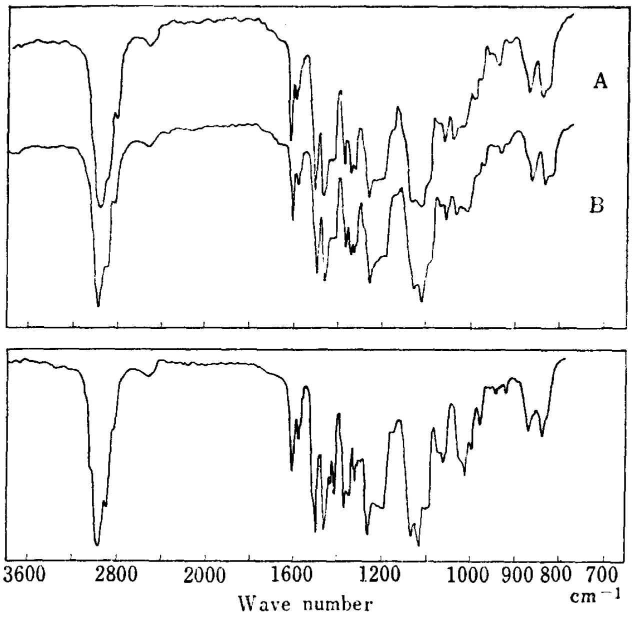
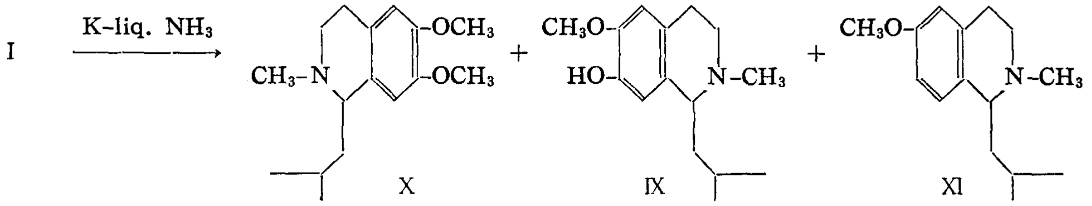


Fig. 1. Infrared Absorption Spectra (in $CHCl_3$)

Above : Synthesized base
A: I-A; B: I-B
Below : O-Methylisopilocereine

To verify the structure of the base (I) synthesized, the potassium-liq. ammonia cleavage reaction was carried out, where the base——a 1:1 mixture of I-A and I-B——gave O-methyllophocerine (X) and lophocerine (IX) nearly quantitatively with a trace of the 6-methoxy compound (XI). Considering the synthetic route, this result confirms that the structure of the base synthesized is I.



From the result of. potassium-liq. ammonia cleavage1) of O-methylisopilocerine, it was deduced that the structure of the base should be I or XII. However, since O-methylisopilocereine differed from the synthesized I, it could not have structure (I) and so it must have formula (XII), which is that assigned to O-methylpilocereine and O-methylpiloceredine by Djerassi, *et al.*2)

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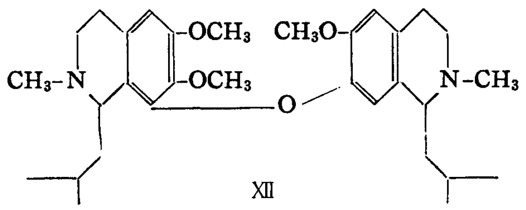
*4 PPC : paper chromatography. MPC : multi-buffered paper chromatography. PEP : paper electrophoresis. TLC : thin layer chromatography. Cf. the footnote in Part II.1)

1) Part II. This Bulletin, **11**, 1477 (1963).

2) C. Djerassi, S.K. Figdor, J.M. Bobbitt, F.X. Markley : J. Am. Chem. Soc., **79**, 2203 (1957); C. Djerassi, T. Nakano, J.M. Bobbitt : Tetrahedron, **2**, 58 (1958).



XII

Experimental[*5]

β-Nitro-2-bromo-3,4-dimethoxystyrene (III)——A solution of 30 g. of 2-bromoveratraldehyde, 30 ml. of CH_3NO_2, and 10 g. of $AcONH_4$ in 80 ml. of AcOH was refluxed for 2 hr. The reaction mixture was then poured into 1 L. of ice water to form a crystalline precipitate. Recrystallization from Me_2CO-MeOH gave 27.0 g. of yellow plates, m.p. 96∼98°, (77%). *Anal.* Calcd. for $C_{10}H_{10}O_4NBr$: C, 41.68; H, 3.52. Found : C, 41.48; H, 3.53.

2-Bromo-3,4-dimethoxyphenethylamine (IV)——Electrolytic reduction of 10 g. of III (Anode solution: 20% H_2SO_4. Cathode : Lead plate, 100 cm². Cathode solution : A mixture of 260 ml. of MeOH, 100 ml. of AcOH, 320 ml. of tetrahydrofuran, and 40 ml. of conc. HCl. Current : 7 A. 1.5 hr. 17∼20°) gave an oily base, which was converted into the oxalate and recrystallized from MeOH to yield 6.05 g. of IV oxalate as colorless plates, m.p. 205∼206° (decomp.), (50%). *Anal.* Calcd. for $C_{10}H_{14}O_2NBr\cdot(COOH)_2$: C, 41.16; H, 4.61. Found : C, 41.33; H, 4.97.

The neutral oxalate was also found on treatment of the amine with a half mole of oxalic acid and recrystallized from MeOH as colorless needles, m.p. 234∼235° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}O_2NBr\cdot\frac{1}{2}(COOH)_2$: C, 43.29; H, 4.96. Found : C, 43.13; H, 5.04.

N-(2-Bromo-3,4-dimethoxyphenethyl)isovaleramide (V)——To a stirred mixture of 10% KOH and an ethereal solution of IV (regenerated from 5.5 g. of the oxalate) was added dropwise an ethereal solution of 2.2 g. of isovaleryl chloride with stirring. After 1 hr., the Et_2O layer was separated from the aqueous layer, washed successively with dil. HCl and dil. KOH, dried over anhyd. $MgSO_4$, and evaporated. The product was recrystallized from Me_2CO-EtOH yielding 5.2 g. of colorless needles, m.p. 104∼105°, (96%). *Anal.* Calcd. for $C_{15}H_{22}O_3NBr$: C, 52.34; H, 6.45. Found : C, 52.08; H, 6.39.

1-Isobutyl-5-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline (VI)——A solution of 6.8 g. of V and 30 ml. of $POCl_3$ in 30 ml. of dry toluene was refluxed for 3 hr. The solvent and the excess of $POCl_3$ were removed by evaporation under reduced pressure. After addition of 10% KOH, the product was taken up in Et_2O, and the Et_2O solution was dried over anhyd. K_2CO_3 and evaporated. The residue crystallized on treatment with Et_2O-hexane to give 5.2 g. of colorless plates, m.p. 76∼77°, (81%). *Anal.* Calcd. for $C_{15}H_{20}O_2NBr$: C, 55.22; H, 6.18. Found : C, 55.52; H, 6.14.

Hydrochloride : Recrystallized from MeOH. Colorless plates, m.p. 174∼176° (decomp. darkened from 165°). *Anal.* Calcd. for $C_{15}H_{20}O_2NBr\cdot HCl$: C, 49.67; H, 5.85; N, 3.86. Found : C, 49.37; H, 5.86; N, 3.70.

1-Isobutyl-5-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII)——A solution of 5.2 g. of VI in 100 ml. MeOH was treated with 2.5 g. of $NaBH_4$. The solution was stirred at room temperature for 1 hr. The solvent was removed under reduced pressure and after addition of H_2O the product was extracted with Et_2O. The Et_2O extract was dried over anhyd. K_2CO_3 and evaporated leaving 5.0 g. of a colorless, oily product. It was converted into the oxalate and recrystallized from MeOH-EtOH to yield 6.0 g. of colorless needles, m.p. 205∼206° (decomp.), (90%). *Anal.* Calcd. for $C_{15}H_{22}O_2NBr\cdot(COOH)_2$: C, 48.81; H, 5.79. Found : C, 48.77; H, 5.69.

1-Isobutyl-2-methyl-5-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII)——A mixture of 4.7 g. of VII (liberated from 6.0 g. of the oxalate), 40 ml. of 30% HCHO, and 40 ml. of 98% HCOOH was heated for 4 hr. in a boiling water bath. Usual acid-alkali treatment of the reaction mixture afforded 6.0 g. of the N-methyl compound, which was converted into the oxalate and recrystallized from EtOH to give 5.2 g. of colorless, rhombic plates, m.p. 164∼165° (decomp.), (84%). *Anal.* Calcd. for $C_{16}H_{24}O_2NBr\cdot(COOH)_2$: C, 50.01; H, 6.07. Found : C, 49.96; H, 6.29.

The picrate was prepared in the usual manner and recrystallized from EtOH as yellow, rhombic plates, m.p. 172∼174°. *Anal.* Calcd. for $C_{16}H_{24}O_2NBr\cdot C_6H_3O_7N_3$: C, 46.24; H, 4.77. Found : C, 46.49; H, 4.86.

1,1′-Diisobutyl-2,2′-dimethyl-6,6′,7-trimethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-5,7′-oxydiisoquinoline (I)——A mixture of 5.12 g. of VIII (regenerated from 6.48 g. of the oxalate), 4.25 g. of lophocerine (IX) (regenerated from 5.00 g. of the oxalate), 20 ml. of dry pyridine, 4.0 g. of finely pulverized anhyd. K_2CO_3, 0.5 g. of Cu powder, and 0.2 g. of KI was heated in a slow stream of N_2 in an oil bath (153∼

[*5] All melting points are uncorrected.

155°). After 8 hr., 0.2 g. of Cu and 1.0 g. of K_2CO_3 were added; after 30 hr., 0.5 g. of Cu was added. The reaction mixture was examined by PPC from time to time. At the beginning of the reaction, the mixture showed two spot at Rf 0.80 (VIII) and 0.70 (IX). As the reaction proceeded, the spot at Rf 0.80 became weaker and a new spot appeared at Rf 0.63 (Debromo-compound (X) shows a spot at the asme position as IX, Rf 0.70). After 35 hr., the spot at Rf 0.80 almost disappeared. The reaction mixture was filtered, and the residue was washed with $CHCl_3$. The combined filtrates were evaporated under reduced pressure, and the residue was dissolved in Et_2O. The solution was fractionated in the usual manner to afford 5.71 g. of the non-phenolic base and 1.83 g. of the phenolic base. The latter, when treated with oxalic acid in EtOH, gave 1.81 g. of IX oxalate, m.p. 213~214°(decomp.).

Vacuum distillation of the non-phenolic, basic fraction gave 1.90 g. of a low-boiling material (b.p$_1$ 160~165°), which was converted into the oxalate yielding 2.17 g. of the debromo-compound (X) oxalate, m.p. 136~137°. The distillation residue was chromatographed on Al_2O_3(1 × 10 cm.) with a hexane-Et_2O (1:1) mixture. The eluted base was dissolved in $CHCl_3$, washed with pH 5.7 buffer solution and then extracted with pH 3.9 buffer solution. Basification of the pH 3.9 buffer extracts and extraction with Et_2O gave an oily residue, which was again chromatographed on Al_2O_3(1 × 30 cm.). After a trace of X had been eluted with hexane, successive elution with hexane, hexane-benzene, benzene, and benzene-Et_2O afforded forty-three fractions (Fract. 9~51) showing a same spot on PPC (Rf 0.63). Total weight of the base was 1.59 g. (24%). These fractions also showed a single spot on MPC (pH 3.6) and on PEP, but two spots were observed on TLC. Therefore the fractions were further submitted to chromatographic separation.

Fractions 9~34 were combined (0.35 g.) and chromatographed on Al_2O_3(0.8 × 20 cm.). The first two fractions eluted with a hexane-Et_2O mixture (19:1) showed a single spot (the higher one) on TLC and gave 33 mg. of a colorless, oily base (I-A).

Fractions 46~51 (0.37 g.) were also chromatographed on Al_2O_3(0.8 × 20 cm.) and the last four fractions eluted with a hexane-Et_2O mixture (9:1) gave 12 mg. of a colorless, oily base which showed a single spot (the lower one) on TLC (I-B).

These two bases were considered to be the diastereomers of I, because their IR spectra (in $CHCl_3$) were essentially identical. UV: λ_{max}^{EtOH} 283 mμ (log ε 3.72) (I-A). Crystallizations of them and of their derivatives were attempted without success.

Cleavage of I by Potassium in Liquid Ammonia——Fractions 35~45 of the above described chromatography of I afforded 864 mg. of the oily base which was shown by TLC to be a nearly 1:1 mixture of diastereomers I-A and I-B.

A 200 mg. portion of the oily base was allowed to react with K (100 mg.) in 200 ml. of liq. NH_3 at −58~−53° for 3 hr. Treatment of the reaction mixture in the usual manner gave 94 mg. of non-phenolic, basic and 95 mg. of phenolic, basic fractions.

The non-phenolic, basic fraction was treated with picric acid and recrystallized from EtOH to yield 150 mg. of O-methyllophocerine (X) picrate as yellow plates, m.p. 184~185°, identity of which was shown by mixed melting point and IR comparison (in Nujol) with an authentic sample. *Anal.* Calcd. for $C_{16}H_{25}O_2N \cdot C_6H_3O_7N_3$: C, 53.65; H, 5.73. Found: C, 53.91; H, 5.96.

The free base (15 mg.), recovered from the mother liquor, was chromatographed on Al_2O_3(0.4 × 10 cm.) and eluted with hexane-Et_2O(19:1). Fract. 1~2 were converted into the picrate and washed with EtOH. The picrate (1 mg.) melted at 153~154° and showed no depression of the melting point on admixture with a specimen of 1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XI) picrate (m.p. 154~155°). Fract. 3~6 afforded additional 15 mg. of X picrate, m.p. 184~185°.

The IR spectrum (in $CHCl_3$) of the bisected, phenolic base was shown to be identical with that of lophocerine (IX). When treated with picric acid and recrystallized from EtOH, 172 mg. of IX picrate was obtained as yellow, rhombic plates, m.p. 194~195°. Identity was confirmed 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, 52.43; H, 5.77.

Further examination of the mother liquor gave no other base.

Summary

Base (I), which had been presumed to be O-methylisopilocereine, was synthesized and two racemic diastereomers were isolated. However, the fact that these bases are not O-methylisopilocereine suggested that the latter should be represented by formula (XII), which had been assigned to O-methylpilocereine and O-methylpiloceredine.

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