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

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In the preceding paper[*3] the author reported the synthesis of Ib from a dialdehyde and the observation that the base (Ib) synthesized there was quite similar to O-methylisopilocereine and not to O-methylpilocereine in their infrared spectra and chromatographic behaviours. This paper deals with the synthesis of Ib in an alternative route, which assured the observation described above.

1-Isobutyl-2-methyl-8-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII) was prepared from 5-bromoveratraldehyde as shown in Chart 1. Ullmann condensation between VII and lophocerine (VIII) was performed in pyridine solution in the presence of potassium carbonate, potassium iodide, and copper powder and, after removal of the starting materials and the debromination product (IX) by vacuum distillation, the product was purified by alumina chromatography to give an oily base which showed a single spot on PPC.[*4] Repeated alumina chromatography of this product resulted in separation of two components, needles melting at 89~91° and pillars melting at 122~123°, both

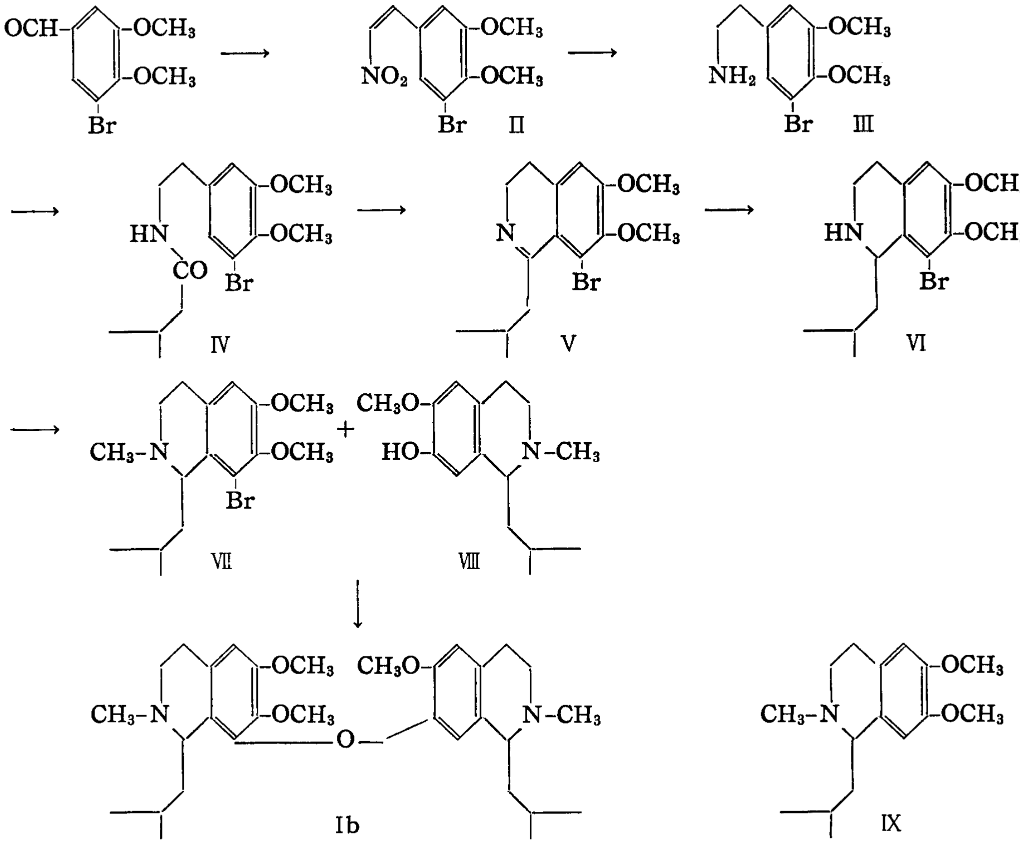

Chart 1.

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[*3] Part V. (2). This Bulletin, **11**, 1495 (1963).

[*4] PPC : paper chromatography. MPC : multi-buffered paper chromatography. PEP : paper electrophoresis. Cf. the footnote in Part II (this Bulletin, **11**, 1477 (1963)).

NII-Electronic Library Service

showing the analytical data coincident with the formula (Ib). They have identical infrared spectra in chloroform solution and identical ultraviolet spectra. They also showed the same behaviours on PPC, MPC, and PEP.*[4] However, several differences were found between their infrared spectra when measured in potassium bromide disk and a depression of the melting point was observed on admixture. Since no interconversions of the melting points or the crystalline forms were observed on cross seeding, the possibility of dimorphism was excluded and they were considered to be diastereomers.

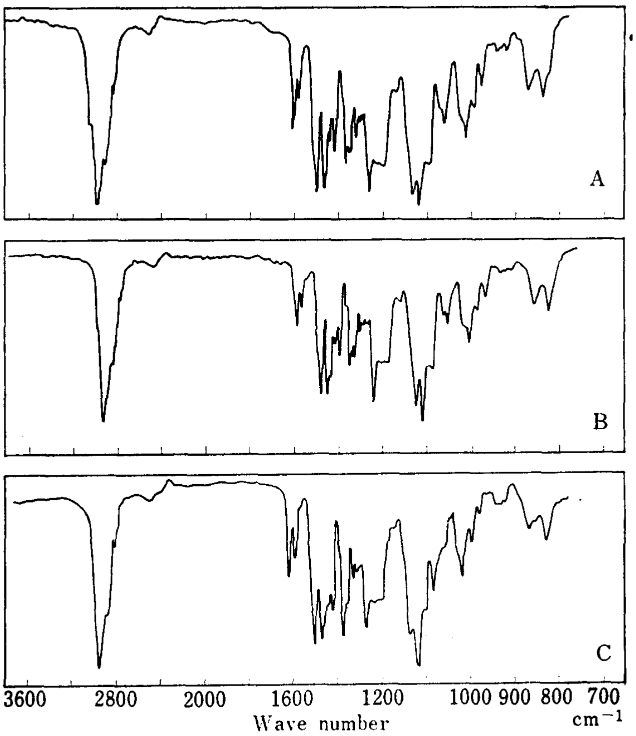
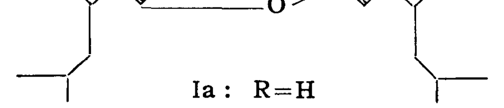


Fig. 1. Infrared Absorption Spectra (in $CHCl_3$)

A : O-Methylisopilocereine
B : Synthetic base (Ib)
C : O-Methylpilocereine

Of these two racemic diastereomers, the needles melting at 89~91° did not depress the melting point of an authentic sample of O-methylisopilocereine (m.p. 91~92°) and their infrared spectra were quite identical even when measured in potassium bromide disk. On the other hand, the pillars melting at 122~123° was proved to be the same compound which was obtained by another synthetic route reported in the preceding paper.*[3] Non-identity of both compounds with O-methylpilocereine was shown in their infrared spectra, chromatographic data and by the melting point depressions on admixture.

These results indicate that the bases synthesized here have correctly the structure (Ib) and that O-methylisopilocereine should be also represented by this formula. This conclusion means that, if one approves Djerassi's formula (Ia)1) of pilocereine and pilroceredine, four racemic bases, namely O-methylpilocereine, O-methylpiloceredine, O-methylisopilocereine and the pillars melting at 122~123°, would have to be represented by the same formula (Ib). However, this formula has only two asymmetric carbons and at most two kinds of racemic diastereomers can be considered.



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

Therefore one more asymmetric center, *e.g.* a molecular asymmetry about the diphenyl ether linkage, must be taken into consideration to account for this stereoisomerism. This assumption, however, seems improbable and the formula (Ia) of pilocereine and piloceredine must be reexamined.

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1) 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).

NII-Electronic Library Service

Experimental*5

β-Nitro-5-bromo-3,4-dimethoxystyrene (II)——A mixture of 60 g. of 5-bromoveratraldehyde, 50 ml. of CH_3NO_2, 20 g. of $AcONH_4$, and 160 ml. of AcOH was refluxed for 2 hr. The reaction mixture was then poured into 2 L. of ice water. The crystalline precipitate was collected and recrystallized from AcOEt yielding 39 g. of yellow needles, m.p. 157~158°, (55%). (rec.[2] m.p. 159°).

5-Bromo-3,4-dimethoxyphenethylamine (III)——The nitrostyrene (Ⅱ) (10.0 g.) was converted into the amine (Ⅲ) by electrolytic reduction as described for the preparation of 2-bromo-compound.[3] The oxalate of the amine was recrystallized from EtOH to give 8.2 g. of colorless plates, m.p. 195~196° (decomp.), (68%). *Anal.* Calcd. for $C_{10}H_{14}O_2NBr\cdot(COOH)_2$: C, 41.16; H, 4.61. Found : C, 41.43; H, 4.85.

N-(5-Bromo-3,4-dimethoxyphenethyl)isovaleramide (IV)——A mixture of 10% KOH and an ethereal solution of Ⅲ (liberated from 25.0 g. of the oxalate) was allowed to react with 11.0 g. of isovaleryl chloride as described earlier for 2-bromo-compound. Recrystallization of the product from benzene afforded 24.2 g. of colorless needles, m.p. 71~72°, (98%). *Anal.* Calcd. for $C_{15}H_{22}O_3NBr$: C, 52.34; H, 6.45. Found : C, 52.32; H, 6.52.

1-Isobutyl-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline (V)——A mixture of 24.2 g. of Ⅳ, 50 ml. of $POCl_3$, and 100 ml. of toluene was refluxed for 3 hr. The solvent and the the excess of the reagent were removed under reduced pressure, and acid-alkali treatment of the residue yielded 21.5 g. of V as a colorless oil (94%). The characterization was performed as following derivatives. Picrate: recrystallized from Me_2CO-EtOH as yellow, rhombic plates, m.p. 204~205°. *Anal.* Calcd. for $C_{15}H_{20}O_2NBr\cdot C_6H_3O_7N_3$: C, 45.42; H, 4.18. Found : C, 45.70; H, 4.23.

Oxalate : recrystallized from MeOH-EtOH as colorless needles, m.p. 149~150°(decomp.). *Anal.* Calcd. for $C_{15}H_{20}O_2NBr\cdot(COOH)_2\cdot H_2O$: C, 47.01; H, 5.57. Found : C, 46.83, 47.13; H, 5.32, 5.59.

1-Isobutyl-8-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI)——To a solution of V (21.5 g.) in 100 ml. of MeOH was added 10.0 g. of $NaBH_4$ and the mixture was allowed to stand at room temperature for 2 hr. The product was dealt by the usual method to afford 22.0 g. of a syrupy base, crystallization of which from Et_2O-hexane gave 13.0 g. of colorless plates, m.p. 75~76°. The mother liquor was converted into the hydrochloride and recrystallized from MeOH to give colorless needles, m.p. 243~244°. This hydrochloride was again converted into the free base and 4.2 g. of plates, m.p. 75~76°, was obtained (Total yield : 79%). *Anal.* Calcd. for $C_{15}H_{22}O_2NBr$: C, 54.88; H, 6.76. Found : C, 55.13; H, 6.71.

The oxalate was prepared in EtOH solution and recrystallized from the same solvent as colorless, rhombic plates, m.p. 97~99°(decomp.). *Anal.* Calcd. for $C_{15}H_{22}O_2NBr\cdot(COOH)_2\cdot H_2O$: C, 46.80; H, 6.01. Found : C, 46.99, 47.25; H, 6.11, 6.26.

1-Isobutyl-2-methyl-8-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII)——A mixture of 12.5 g. of Ⅵ, 60 ml. of 99% HCOOH, and 60 ml. of 30% HCHO was heated for 4 hr. in a boiling water bath and then evaporated. After the usual acid-alkali treatment, 13 g. of a colorless, oily product was obtained, which afforded 16.0 g. of the oxalate as colorless pillars, m.p. 180~181°(decomp.), (97%). Recrystallization from MeOH-EtOH gave an analytical sample, m.p. 181~182°(decomp.). *Anal.* Calcd. for $C_{16}H_{24}O_2NBr\cdot(COOH)_2$: C, 50.01; H, 6.07. Found : C, 50.30; H, 6.24.

The picrate was prepared in EtOH solution and recrystallized from Me_2CO-EtOH as yellow pillars, m.p. 170~172°. *Anal.* Calcd. for $C_{16}H_{24}O_2NBr\cdot C_6H_3O_7N_3$: C, 46.24; H, 4.77. Found : C, 46.50; H, 4.68.

O-Methylisopilocereine and its Diastereomer (Ib)——The free bases, regenerated from 6.70 g. of Ⅶ oxalate and 5.00 g. of Ⅷ oxalate, were dissolved in 10 ml. of dry pyridine and 4.0 g. of finely powdered, anhyd. K_2CO_3, 0.5 g. of Cu powder, and 0.2 g. of KI were added. The mixture was refluxed with stirring in an oil bath at 154~155° in a slow current of N_2 and examined by PPC from time to time. Just like the cases of 5-bromo-compound, the reactants showed two spots on PPC. *i.e.* Rf 0.80 (Ⅶ) and 0.70 (Ⅷ); the spot of Ⅶ became weaker as the reaction proceeded and almost disappeared after 45 hr. while appearance of a new spot at Rf 0.63 was observed. The reaction mixture was filtered and the residue was washed with $CHCl_3$. The combined filtrates were evaporated and fractionated in the usual manner to yield 4.71 g. of an oily, non-phenolic base, while the phenolic, basic fraction afforded 1.20 g. of the oxalate of recovered lophocerine (Ⅷ).

The non-phenolic, basic fraction was chromatographed on Al_2O_3 (1 × 5 cm.) with benzene and then 3.55 g. of a low-boiling material (b.p$_{0.5}$ 140~145°) was removed by distillation, which was converted

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*5 All melting points are uncorrected.

[2] M. Tomita, H. Watanabe : Yakugaku Zasshi, **58**, 783 (1938); H. Kondo, H. Kataoka, Y. Hayashi, T. Uchibori : Ann. Rept. ITSUU Lab. (Tokyo), **9**, 1 (1958).

[3] Part Ⅳ. This Bulletin, **11**, 1491 (1963).

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into the oxalate yielding 3.74 g. of O-methyllophocerine (IX) oxalate, m.p. 136∼137° (debromination product). The residue on distillation was dissolved in Et_2O and the solution was filtered and evaporated. The residue was chromatographed on Al_2O_3 (1 × 10 cm.) and, after 31 mg. of VII and 26 mg. of IX were eluted with a benzene-hexane (1:1) mixture, continued elution with hexane-benzene and with benzene afforded 433 mg. of the oily base (Ib) which showed a single spot on PPC (Rf 0.63) (6%).

This compound was chromatographed again on Al_2O_3 (0.8 × 25 cm.) and eluted with hexane-benzene (1:1, Fract. 1∼15; 1:2, Fract. 16∼22), benzene (Fract. 23∼36), and benzene-$CHCl_3$ (9:1) (Fract. 37∼44). Upon treatment with hexane, Fract. 1∼5 (39 mg.) gave needles melting at 75∼85°, which on repeated chromatography on deactivated Al_2O_3[*6] with hexane yielded colorless needles, m.p. 89∼91°. This compound did not depress the melting point of an authentic specimen of O-methylisopilocereine (m.p. 91∼92°). The IR spectra (in $CHCl_3$ solution and in KBr disk) were also identical with those of the specimen. *Anal.* Calcd. for $C_{31}H_{46}O_4N_2$: C, 72.90; H, 9.08; N, 5.49. Found : C, 73.10; H, 9.26; N, 5.41. UV : λ_{max}^{EtOH} 284 mμ (log ε 3.69).

Fract. 37∼44 (63 mg.) afforded pillars, m.p. 115∼123°, on treatment with hexane, which were recrystallized three times from hexane to yield 45 mg. of colorless pillars, m.p. 122∼123°. Identification with the pillars of Ib, m.p. 122∼123°, reported in the preceding paper[*3] was accomplished by mixed melting point and IR comparison (KBr disk). *Anal.* Calcd. for $C_{31}H_{46}O_4N_2$: C, 72.90; H, 9.08; N, 5.49. Found : C, 72.99; H, 9.30; N, 5.71. UV : λ_{max}^{EtOH} 284 mμ (log ε 3.69).

The IR spectra of the needles and the pillars in $CHCl_3$ solution were quite identical with each other, but apparently different when measured in KBr disk. A marked depression of the melting point was observed on admixture of these two bases. Their melting points and crystalline forms could not be interconverted by cross seeding.

Summary

Base (Ib) was synthesized by the Ullmann condensation between VII and VIII, and the two racemic diastereomers were obtained in crystalline states. One of them was proved to be O-methylisopilocereine, while the other was identified with the diastereomer obtained by another synthetic method. Non-identities of them with O-methylpilocereine, to which the formula (Ib) had been inadequately assigned, were also proved.

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

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