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230. Kiyoshi Bessho*1,*2 : Studies on Pilocereine and Related Compounds. V.*3 Synthesis of O-Methylisopilocereine. (2).

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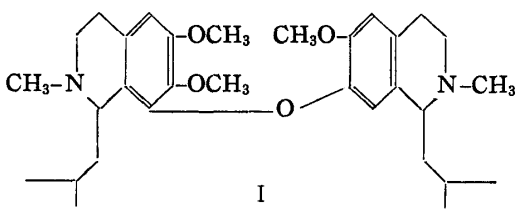
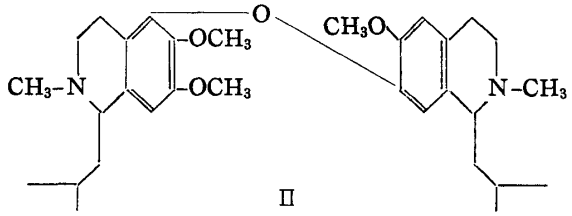
The result of potassium-liq. ammonia cleavage of O-methylisopilocereine showed that the structure of this compound was either I or II,[1] but when compound (II) was synthesized, it was not identical with O-methylisopilocereine.*3 However, the conclusion from this that O-methylisopilocereine should be represented by formula (I) was inconsistent with Djerassi's assignments of O-methylpilocereine[2] and O-methylpiloceredine[3] to the same formula (I) because only two racemic diastereomers are possible for I. The author achieved the synthesis of I to resolve this problem.



I



II

For the synthesis of I, two synthetic schemes are possible; one is the isoquinoline cyclization of a diphenyl ether derivative (VI) and the other is the formation of a diphenyl ether linkage by an Ullmann condensation of two isoquinoline bases. Diamine (V), a key compound in the former scheme, was prepared by Kondo, *et al.*[4] and by Whaley, *et al.*[5] The author also prepared V from the dialdehyde (III) according to the description of Kondo, *et al.*

A Schotten-Baumann condensation of V with isovaleryl chloride afforded the amide (VI), and this was submitted to Bischler-Napieralski cyclization to yield the 3,4-dihydroisoquinoline (VII) which was characterized as a dipicrate, m.p. 198~200°(decomp.). The formation of a mixture of diastereoisomeric tetrahydroisoquinolines (VIII) might be expected on reduction of VII. In practice, sodium borohydride reduction of VII gave an oily base, from which fine needles gradually separated on standing. Although separation of this crystalline tetrahydroisoquinoline compound from the oily substance was very difficult because of their high solubility in various solvents, the separation was achieved by several recrystallizations from an ether-cyclohexane mixture to give a small amout of pure crystalline compound, m.p. 134~135°. This compound was ascertained from its elemental analysis and ultraviolet spectrum to be one of the racemic diastereomers of VIII. On treatment with formaldehyde and formic acid, it gave a N-methyl compound as colorless pillars, m.p. 122~123°. Although its analytical data agreed with formula (I) and the ultraviolet spectrum was identical with that of O-melhylpilocereine, its infrared spectrum in chloroform solution, its chromatographic behaviors (PPC, Rf 0.63; MPC,

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*3 Part IV. (1). This Bulletin **11**, 1491 (1963).

1) Part II, *Ibid.*, **11**, 1477 (1963).
2) C. Djerassi, S. K. Figdor, J. M. Bobbitt, F. X. Markley : J. Am. Chem. Soc., **79**, 2203 (1957).
3) C. Djerassi, T. Nakano, J. M. Bobbitt : Tetrahedron, **2**, 58 (1958).
4) H. Kondo, H. Kataoka, Y. Baba : Ann. Rept. ITSUU Lab. (Tokyo), **5**, 8 (1954); H. Kondo, H. Kataoka, K. Kigasawa : *Ibid.*, **6**, 13 (1955); H. Kataoka : *Ibid.*, **8**, 1 (1957).
5) W. M. Whaley, L. N. Starker, W. L. Dean : J. Org. Chem., **19**, 1018 (1954).

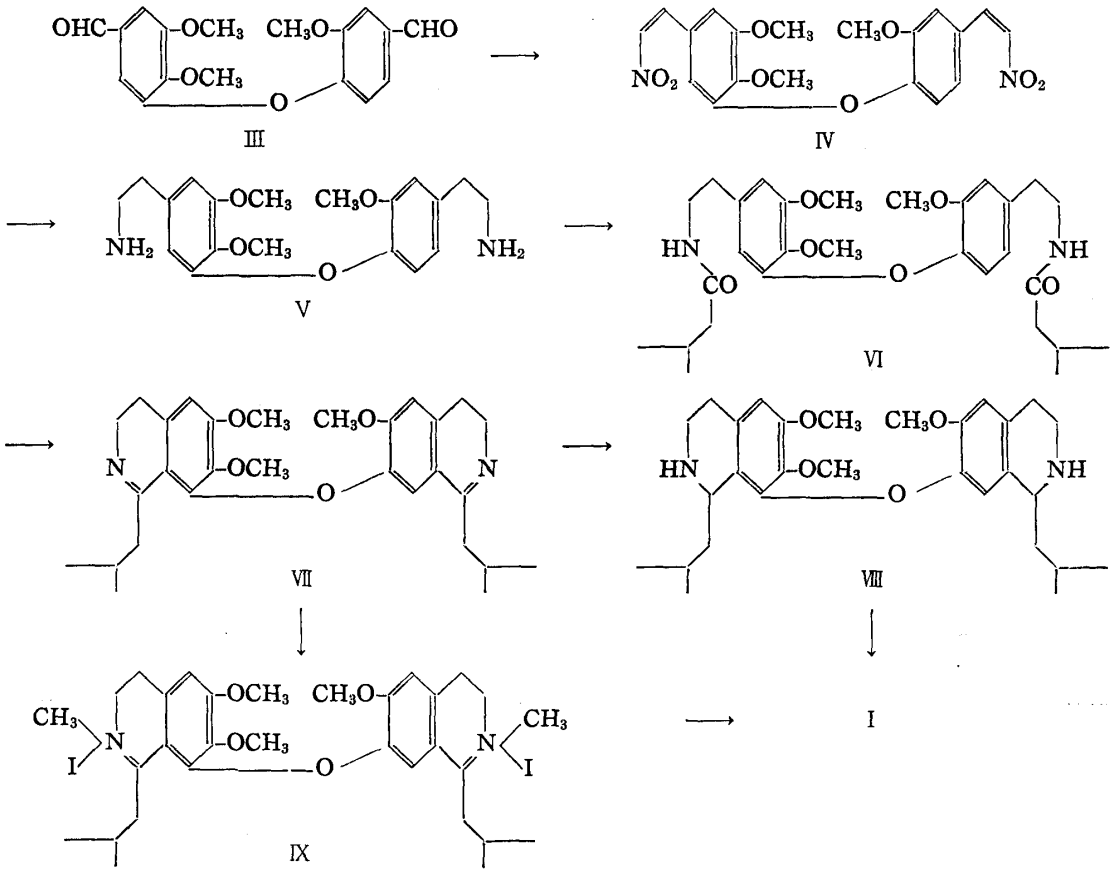

Chart 1.

pH 3.8~3.6)*4 and melting point were different from those of the latter (Rf 0.45; pH 4.4; m.p. 153~155°) and the mixed melting point showed marked depression. Also it is apparent that the base synthesized is not O-methylpiloceredine (m.p. 141~142°) since the latter has been reported to show an identical infrared spectrum in chloroform solution with O-methylpilocereine.

On the other hand, when compared with O-methylisopilocereine (m.p. 91~92°), these pillars showed good coincidence on PPC, on MPC, in their ultraviolet spectra, and even in their infrared spectra in chloroform solution. However, the melting points were different and the mixed melting point was apparently depressed.

The oily tetrahydroisoquinoline compound (VIII), which, as mentioned above, was believed to be a mixture of diastereomers, gave an oily N-methyl base (I) upon N-methylation, while sodium borohydride reduction of the dihydroisoquinoline methiodide (IX), m.p. 205~206° (decomp.), gave the same oily N-methyl base (I). These oily bases had identical infrared spectra in chloroform solution with the pillars above described (and also with O-methylisopilocereine), suggesting that they were mixtures of diastereomers of I.

However, on Bischler-Napieralski cyclization of VI in this synthesis, it was possible that cyclization might occur at the (b)-position instead of the (a)-position on the benzene ring, as shown in Chart 2. If this were the case, the final product obtained would be X. This suspicion was excluded by the fact that potassium-liq. ammonia cleavage of the oily base (I) afforded lophocerine (XI) and O-methyllophocerine (XII) as bisected bases in nearly quantitative yield. The latter was characterized as its picrate, m.p. 184~

*4 PPC: paper chromatography. MPC: multi-buffered paper chromatography. Cf. the footnote in Part II.[1]

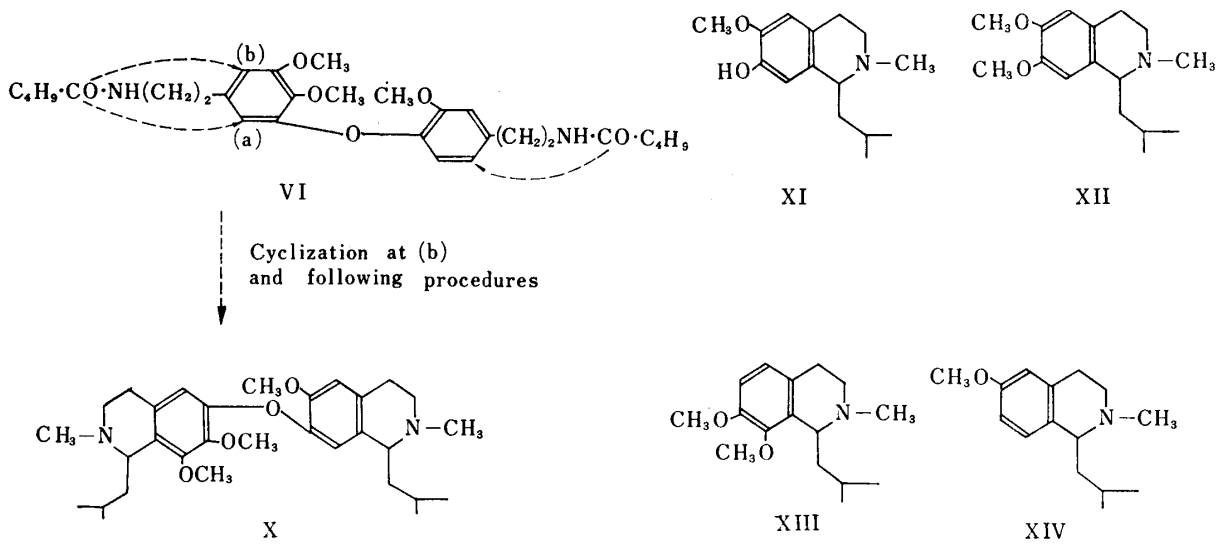

Chart 2.

185°, and methiodide, m.p. 196~198°, the melting points of which were apparently different from those of XIII (picrate, m.p. 133~135°; methiodide, m.p. 165~166°)[6] which might be expected to be a bisected base of X. On careful examination of the mother liquor of the bisected, non-phenolic base traces were found of 1-isobuthyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XIV) (identified as its picrate, m.p. 153~154°) and a kryptophenolic base $C_{15}H_{23}O_2N$, m.p. 101~102°. The structure of the latter has not been investigated.

These results proved that the structure of the base synthesized is I. In view of the chromatographic data and the infrared spectrum of this synthetic base it was concluded that formula (I) should be assigned to O-methylisopilocereine and not to O-methylpilocereine.

Experimental*5

4′,5-Bis(2-nitrovinyl)-2,2′,3-trimethoxydiphenyl Ether (IV)——i) To a ice-cooled solution of 6.0 g. of dialdehyde (III) (m.p. 101~102°) and 3.5 g. of CH_3NO_2 in 40 ml. of MeOH was added dropwise 100 ml. of a MeOH solution of KOH (6 g.) with stirring. After 1 hr., the reaction mixture was poured nito cold 5% HCl, and the precipitate was collected by suction. Recrystallization from Me_2CO-MeOH yielded 5.23 g. of yellow, rhombic plates, m.p. 181~183°, (69%). (rec.[4] m.p. 180~183°).

ii) A mixture of 0.5 g. of III, 0.5 ml. of CH_3NO_2, 0.2 g. of $AcONH_4$, and 2 ml. of AcOH was refluxed for 2 hr. and then poured into 50 ml. of cold H_2O. The precipitate was purified by the usual method and there was obtained 360 mg. of yellow crystals, m.p. 180~181°, (57%).

4′,5-Bis(2-aminoethyl)-2,2′,3-trimethoxydiphenyl Ether (V)——To a vigorously stirred suspension of 3.0 g. of $LiAlH_4$ in tetrahydrofuran was added a solution of 3.0 g. of IV in the same solvent, and the mixture was allowed to react for 7 hr. in a water bath at 70°. After decomposition of the excess of hydride with dil. NaOH, the precipitate was filtered off and washed with $CHCl_3$. The residue on evaporation of the combined filtrate was purified by acid-alkali treatment to give the oily amine. Addition of a 1% ethereal solution of oxalic acid to an ethereal solution of the amine caused the dioxalate to precipitate. The yield of V dioxalate, m.p. 101~104° (decomp.) was 2.12 g. (65%). (rec.[4] m.p. 106~109°).

4′,5-Bis(2-isovaleramidoethyl)-2,2′,3-trimethoxydiphenyl Ether (VI)——i) To a mixture of 10% KOH (30 ml.) and $CHCl_3$ solution of the amine (V) (regenerated from 5.21 g. of the oxalate) was added dropwise a $CHCl_3$ solution (50 ml.) of 5.0 g. of isovaleryl chloride with stirring. The stirring was further continued for 1 hr., then the $CHCl_3$ layer was separated, washed with dil. HCl, dried over anhyd.

*5 All melting points are uncorrected.

6) C. Djerassi, F. X. Markley, R. Ehrlich: J. Org. Chem., **21**, 975 (1956).

K_2CO_3, and evaporated. The residue was chromatographed on Al_2O_3 (1×5 cm.) with benzene-AcOEt (9:1) to yield 4.95 g. of the amide as a colorless oil (85%).

ii) A solution of 0.36 g. of V (regenerated from the oxalate) and 0.3 g. of isovaleric acid in 5 ml. of toluene was refluxed for 15 hr.; the H_2O formed in the reaction was removed by H_2O take-off condensor. After evaporation under reduced pressure, the residue was dissolved in $CHCl_3$. The solution was washed with dil. HCl and then with dil. KOH, dried over anhyd. K_2CO_3, and evaporated leaving 0.33 g. of the oily amide (45%). IR spectrum (in $CHCl_3$) of the product was identical with that of the amide obtained in i).

3,4-Dihydroisoquinoline Compound (VII)——A mixture of 2.44 g. of the amide (VI), 20 ml. of toluene, and 20 ml. of $POCl_3$ was refluxed for 2 hr. The solvent and the excess of the reagent were removed by evaporation under reduced pressure, and the residue was washed three times with petr. ether. After addition of dil. KOH, the product was taken up in Et_2O. The Et_2O solution was washed with pH 5.8 buffer solution and then extracted with pH 4.8 buffer solution. The extract was made alkaline and extracted with Et_2O. Evaporation of the Et_2O extract after drying over anhyd. K_2CO_3 yielded 0.95 g. of the oily base (VII) (40%). This base was characterized as the dipicrate which was recrystallized from Me_2CO-MeOH as yellow octahedrons, m.p. 198~200° (decomp.). *Anal.* Calcd. for $C_{29}H_{38}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 52.56; H, 4.74; N, 11.95. Found: C, 52.84; H, 4.78; N, 11.74.

3,4-Dihydroisoquinoline Compound Dimethiodide (IX)——A mixture of 0.15 g. of VII, 2 ml. of MeI, and 2 ml. of MeOH was refluxed for 4 hr. Recrystallization of the product from MeOH-Me_2CO yielded 0.20 g. of pale yellow pillars, m.p. 205~206° (decomp.), (80%). *Anal.* Calcd. for $C_{31}H_{44}O_4N_2I_2 \cdot 2H_2O$: C, 46.63; H, 6.06; N, 3.51; I, 31.85. Found: C, 46.78, 46.77; H, 6.28, 6.10; N, 3.60; I, 32.04.

1,2,3,4-Tetrahydroisoquinoline Compound (VIII)——To a solution of 950 mg. of VII in 15 ml. of MeOH was added portionwise 500 mg. of $NaBH_4$ at room temperature. The product obtained on the usual treatment was chromatographed on Al_2O_3*6 (1×5 cm.) with benzene to yield 900 mg. of tetrahydroisoquinoline compound (VIII) as a colorless, oily material containing fine needles. This substance showed a single spot on PPC and on MPC. A small amount of hexane was added and the crude crystals were collected by suction (180 mg., m.p. 110~121°). Careful recrystallizations from Et_2O-cyclohexane afforded 26 mg. of colorless needles, m.p. 134~135°. *Anal.* Calcd. for $C_{29}H_{42}O_4N_2$: C, 72.16; H, 8.77; N, 5.80. Found: C, 72.15; H, 8.85; N, 5.90. UV: λ_{max}^{EtOH} 283 mμ (log ε 3.72).

The mother liquor, after evaporation of the solvent, gave again the oily material containing fine needles (870 mg.) which was considered as a mixture of the diastereomers of VIII.

1,1′-Diisobutyl-2,2′-dimethyl-6,6′,7-trimethoxy-1,1′, 2, 2′, 3, 3′, 4, 4′-octahyhro-7′,8-oxydiisoquinoline (I)——i) A mixture of 2 ml. of 98% HCOOH, 2 ml. of 30% HCHO, and 18 mg. of the above needles (VIII) was heated for 5 hr. in a boiling water bath and then evaporated under reduced pressure. The residue was purified by usual acid-alkali treatment to give 18 mg. of colorless pillars, m.p. 120~122°. Recrystallization from hexane raised the melting point to 122~123°. *Anal.* Calcd. for $C_{31}H_{46}O_4N_2$: C, 72.90; H, 9.08; N, 5.49. Found: C, 73.06; H, 9.04; N, 5.47. UV: λ_{max}^{EtOH} 284 mμ (log ε 3.70).

This compound depressed the melting points of O-methylpilocereine (m.p. 154~154.5°) and O-methylisopilocereine (m.p. 91~92°) while the IR spectrum (in $CHCl_3$) was identical with that of O-methylisopilocereine, but different from that of O-methylpilocereine.

ii) The mother liquor of VIII above described (870 mg.) was treated with 15 ml. of 98% HCOOH and 15 ml. of 30% HCHO in a similar manner. The crude product was chromatographed on Al_2O_3 (1×5 cm.) with benzene yielding 850 mg. of a colorless, oily base (94%). The IR spectrum (in $CHCl_3$) and Rf value on PPC were identical with those of the crystals (m.p. 122~123°) obtained in i).

iii) To a methanolic solution of 180 mg. of the dimethiodide (IX) was added portionwise 500 mg. of $NaBH_4$, and the mixture was stirred for 1 hr. at room temperature. Evaporation of the solvent and the usual acid-alkali treatment of the residue afforded 100 mg. of the colorless, oily base (86%). The IR spectrum (in $CHCl_3$) and Rf value on PPC were also identical with those of the crystals obtained in i).

Cleavage of Synthetic Base (I) by Potassium in Liquid Ammonia——A solution of 1.02 g. of I (obtained in ii)) in 30 ml. of dry Et_2O was added to 400 ml. of liq. NH_3 kept at −60~−50°, then 0.9 g. of K was added in portions to the mixture with stirring. After 5.5 hr., the reaction mixture was decolored by addition of NH_4Cl and the solvents were allowed to evaporate. The residue was fractionated by the usual method into 500 mg. of non-phenolic, basic and 480 mg. of phenolic basic fractions.

A 100 mg. portion of the phenolic base was treated with 25 mg. of oxalic acid (½ mole equivalent) in EtOH yielding 100 mg. of lophocerine (XI) oxalate as colorless pillars, m.p. 213~214° (decomp.). Identity was established by mixed melting point and IR comparison (in Nujol). *Anal.* Calcd. for $C_{15}H_{23}O_2N \cdot \frac{1}{2}(COOH)_2$: C, 65.28; H, 8.22. Found: C, 65.07; H, 8.50.

*6 Aluminium oxide neutral (Woelm).

Remaining 380 mg. portion of the phenolic base was converted into the picrate and recrystallized from EtOH to yield 600 mg. of XI picrate as yellow plates, m.p. 194~195°. Identification was accomplished 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, 52.45; 5.70.

The non-phenolic base was also converted into the picrate. Yellow plates, m.p. 184~185°, 720 mg. This picrate was identified with O-methyllophocerine (XII) picrate by mixed melting point and IR comparison (in Nujol). *Anal.* Calcd. for $C_{16}H_{25}O_2N \cdot C_6H_3O_7N_3$: C, 53.65; H, 5.73. Found : C, 53.36; H, 5.81.

The methiodide was derived from a portion of the picrate and recrystallized from hexane-Me_2CO as colorless plates, m.p. 196~198°. No depression of the melting point was observed on admixture with a specimen of XII methiodide.

The mother liquor of the picrate of crude non-phenolic base was converted into the free base and chromatographed on Al_2O_3*[7] (0.5 × 20 cm.). The hexane-benzene (1:1) eluate gave 8 mg. of XIV which was identified by IR comparison (in $CHCl_3$) and by mixed melting point determination of the picrate (m.p. 153~154°). Following hexane-benzene (1:1) and benzene eluates gave 75 mg. of XII which afforded 110 mg. of the picrate, m.p. 184~185°. Finally benzene-Et_2O (100:1~9:1) eluted 8 mg. of a base which crystallized on treatment with hexane as colorless plates, m.p. 101~102°. *Anal.* Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30. Found : C, 72.14; H, 9.29. This compound gave positive Gibbs reaction, but was not further examined because of the poor quantity.

Summary

Base (I), the structure of which had been considered to be that of O-methylpilocereine and O-methylpiloceredine, was synthesized from diphenyl ether dicarboxaldehyde (III). One of its racemic diastereomers was isolated in crystalline state. Both the crystalline base (I) and the mixture of its diastereomers had identical infrared spectra with O-methylisopilocereine in chloroform solution. The chromatographic behaviours also suggested that the formula (I) represents O-methylisopilocereine, not O-methylpilocereine.

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